PLACENTAL PATHOLOGY IN INTRAUTERINE GROWTH RESTRICTION AND ITS RELATION TO PERINATAL OUTCOME

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled "**PLACENTAL PATHOLOGY IN INTRAUTERINE GROWTH RESTRICTION AND ITS RELATION TO PERINATAL OUTCOME**" is a bonafide record work done by **Dr. J. REKHA** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for M.D Branch II – Obstetrics & Gynecology.

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DECLARATION

I **Dr. J. REKHA** solemnly declare that the dissertation titled "**PLACENTAL PATHOLOGY IN INTRAUTERINE GROWTH RESTRICTION AND ITS RELATION TO PERINATAL OUTCOME**" has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, and diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.D degree Branch – II (Obstetrics & Gynecology) to be held in April 2012.

Place : Madurai **Dr. J. REKHA**

Date :

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CONTENTS

LIST OF ABBREVIATIONS

LBW	Low Birth Weight
BW	Birth Weight
IUGR	Intra Uterine Growth Restriction
HC	Head Circumference
AC	Abdominal Circumference
FL	Femur Length
HIV	Human Immune Deficiency Virus
DM	Diabetes Mellitus
IGF	Insulin Like Growth Factor
IGFBP	IGF Binding Proteins
BMI	Body Mass Index
SGA	Small for Gestational Age
AGA	Appropriate for Gestational Age
HCG	Human Chorionic Gonadotropin
USG	Ultrasonogram
BPD	Biparietal Diameter
TCD	Transverse Cerebellar Diameter
PI	Ponderal Index
DV	Ductus Venosus
VEGR	Vascular Endothelial Growth factor Receptor

ABSTRACT

PLACENTAL PATHOLOGY IN INTRAUTERINE GROWTH RESTRICTION AND ITS RELATION TO PERINATAL OUTCOME

AIMS AND OBJECTIVES:1)Histopathological examination of placenta of IUGR babies.2)Determine the frequency and cumulative number of placental abnormalities.3)To correlate the data with perinatal outcome in terms of fetal weight, apgar scores and perinatal mortality.

METHOD OF STUDY: Analytical study for a duration of one year.Analysis of the placentas of IUGR babies both microscopically and macroscopically and the results are correlated with the perinatal outcome.

RESULTS AND ANALYSIS:100 placentas of mothers who delivered IUGR babies were analysed.Majority of women were primigravida and in the age group of 21-30 years.45 cases were of unexplained etiology.66 cases had abnormal Doppler flow and 34 cases had gross macroscopic abnormalities of placenta.Histopathological examination revealed multiple placental abnormalities with >3 lesions in 83 cases. Weight of placenta and weight of baby was significantly reduced with 3 or more lesions. The incidence of neonatal complications were significantly increased with multiple lesions.Apgar score at birth was also significantly reduced with multiple lesions. All cases (19 out of 100 cases) of perinatal mortality were in the group with multiple placental lesions.

CONCLUSION: Increased frequency of placental lesions and increased number of lesions were significantly associated with IUGR.Increased number of placental lesions were commonly observed in cases with abnormal Doppler waveforms. Multiple placental lesions were associated with low birth weight, low placental weight, increased frequency of neonatal complications and increased perinatal mortality.

INTRODUCTION

Fetal growth and development remains one of the most complex and fascinating biological processes known. The fetus has been described as a perfect parasite. Under ideal conditions sufficient amounts of maternal nutrients are provided across an uteroplacental circulation that functions efficiently to meet the demands of the growing fetus.

More than merely a conduit for the provision of oxygen and nutrients to the fetus, the placenta actively regulates the passage of substrates necessary for fetal growth and development. Metabolic shifts occurs in virtually all maternal nutrients during pregnancy and the placenta and uteroplacental blood flow plays a key role in the regulation and delivery of the fuels to the fetus.

As gestation advances, a progressive increase in utero placental perfusion occurs. The increase in uterine blood flow parallels increase in weight as pregnancy advances. The appropriate balance and quantity of nutrients is essential for fetal and placental health. Provision of nutrients from the maternal circulation into and through the placenta requires the co-ordinated activity of multiple transport proteins which function differentially in the microvillous

membrane and basal membrane to provide and maintain the specific levels of nutrients necessary for normal fetal growth.

Intrauterine growth restriction connotes failure of the fetus to achieve its growth potential. While genetic abnormalities and chronic fetal infections may cause IUGR, most cases result from placental pathology. Both in vitro and in vivo studies have demonstrated reduced blood volume and transport capacity for nutrients in the placenta of IUGR versus appropriate for gestational age fetus.

The consequences of aberrant fetal growth secondary to placental dysfunction extend beyond the intrauterine phase of existence. A variety of adult chronic illness including cardiovascular disease, dyslipidemia, type II diabetes, obesity are now felt to be a manifestation of fetal malnutrition usually resulting from placental changes precluding optimum function.

The known placental pathology of IUGR infants includes decrease in placental growth, maternal vasculopathy, chronic villitis, increased perivillous fibrin deposition, fetal thrombotic vasculopathy and avascular villi as its secondary features, umbilical cord anomaly, infarct, cytotrophoblast hyperplasia, basement membrane thickening

etc. Histological examination of the placentas from IUGR babies can supplement clinical knowledge of the cause of IUGR.

The present study was undertaken to investigate the pathologic findings regarding the placenta in IUGR babies and to correlate the results with the perinatal outcome. Only through careful gross and microscopic pathologic examination of the placenta can an undiagnosed or suspected condition be identified or diagnosed. This is an essential step in developing effective strategies for the prediction, prevention and possible treatment of growth restricted fetus.

AIM OF THE STUDY

1. Histopathological examination of placenta of term IUGR babies.
2. Determine the frequency and cumulative number of placental abnormalities
3. To correlate the data with the perinatal outcome in terms of fetal weight, apgar scores and perinatal mortality.

REVIEW OF LITERATURE

HISTORICAL REVIEW

It was not until 30 years ago that physicians first recognized that RUNTING – fetal growth restriction was human as well as animal phenomenon.

In 1961, WARKANY and EOLOWORKERS reported normal values for infant weight, length and head circumference and defined fetal growth restriction. In 1962, WHO introduced the term low birth weight (LBW) for all babies weighing less than 2500g as a single category.

GREVENWALD in 1963 reported that one third of LBW infants were mature and their small size could be explained by chronic placental insufficiency. These observations led to the concept that birth weight was governed not only by length of gestation but also by rate of fetal growth.

In 1963 LUBCHENCO and co workers from Denwer published detailed comparisons of gestational age to birth weight in an effort to derive norms for expected fetal size and therefore growth at a given gestational week.

BATALGIA and Coworkers in 1967 then classified small for gestational age infants as those, whose weights were below 10^{th} percentile for gestational age.

UHSER and MCLEAN (1969) proposed that fetal growth standards should be based on normal limits defined by plus or minus two standard deviations.

Not all infants with BW lesser than 10^{th} percentile are pathologically growth restricted, some are simply because of constitutional factors.

In 1969, the nomenclature ‘preterm’ was used to indicate gestational age of less than 37 completed weeks (259days). However LBW babies include both preterm and those born at term but weighting less than 2500gms. Therefore the term IUGR should more strictly refer to fetuses that are small for gestational age and display other signs of chronic hypoxia or failure to thrive. The assignment of a birth weight percentile requires an accurate assessment of gestational age and adjustment for gender, race and altitude.The incidence of LBW in Indian population was estimated to be 28% (Tambyraja, 1992). The incidence of IUGR in Indian population was estimated to be around 3-5%.

INTRA UTERINE GROWTH RETARDATION

Human fetal growth is characterized by sequential patterns of tissue and organ growth, differentiation and maturation. Development is determined by maternal provision of substrate, placental transfer of the substrate and fetal growth potential governed by genome.

IUGR represents a continuum of various conditions that may ultimately result in failure of the fetus to attain its inherent growth potential. Neonates weighing less than 10^{th} percentile for their gestational age are said to have growth restriction. IUGR should strictly refer to fetuses that are small for gestational age that display other signs of chronic hypoxia or failure to thrive.

Compared with appropriately grown counterparts perinatal mortality in growth restricted neonates are 6-10 times greater. Perinatal mortality rates in growth restricted neonates as high as 120 per 1000 for all cases of IUGR and 80 per 1000 after exclusion of anomalous infants have been reported. Perinatal mortality in cases with abnormal Doppler wave form ranges between 40 – 70%. Incidence of IUGR estimated to be around 3-10%.

Classification of IUGR

1. Depending on the time of onset and pathological process

A. Type I / Symmetric IUGR : 20 – 30%

- Growth inhibition in early pregnancy from 4-20 weeks
- Reduced number of cells in fetus
- Overall decreased growth potential
- HC and AC, length, weight below the 10^{th} percentile for gestational age
- Ponderal Index – Normal

B - Type II / Asymmetric IUGR : 70 -80%

- Later than type I – after 28 weeks of gestation
- Cell size is reduced
- Brain sparing effect
- HC - Normal FL - Normal
- AC and Ponderal index low

C - Intermediate IUGR : 5 – 10%

- Combination of type 1 and type 2
- Onset early in second trimester
- Both cell number and cell size reduced

II.Based on Origin of IUGR :

A. Intrinsic : Fetal conditions that cause IUGR

Intrauterine infections, chromosomal disorder

Congenital malformation.

B. Extrinsic : Growth restriction due to elements outside the fetus.

Placental conditions

Maternal diseases

C. Combined

Both intrinsic and extrinsic factors operate.

D. Idiopathic :

Etiology unknown.

AETIOLOGY

FETAL CAUSES :

A. Chromosomal abnormality including trisomy 13,18,21 autosomal deletions and ring chromosomes.

B. Congenital infections: Rubella, cytomegalovirus, varicella and HIV, Malaria, Toxoplasma and Trypanosoma.

C. Structural anamolies: Central nervous system, cardiovascular, gastrointestinal, genitourinary, musculo skeletal.

D. Genetic causes: Agenesis of pancreas, Galactosemia, Phenylketonuria, congenital lipodystrophy.

PLACENTAL CAUSES :

Single umbilical artery

Abnormal placental implantation

Vilamentous umbilical cord insertion

Bilobed placenta

Placental hemangiomas

Microscopic lesions such as thrombosis, infarction, deciduitis, vasculitis, edema, chorioamnionitis.

MATERNAL CAUSES :

Maternal characteristics :

Extremes of maternal age, nulliparity, low maternal weight, H/o IUGR in previous pregnancy.

Maternal diseases : Hypertension, renal diseases, autoimmune disorders, hyperthyroidism and long term insulin dependent

diabetes, respiratory diseases, long standing type 2 DM with vasculopathy.

Maternal smoking

Alcohol and Drugs – Cocaine and opiates

Thrombophilias – Antiphospholipid antibody syndrome

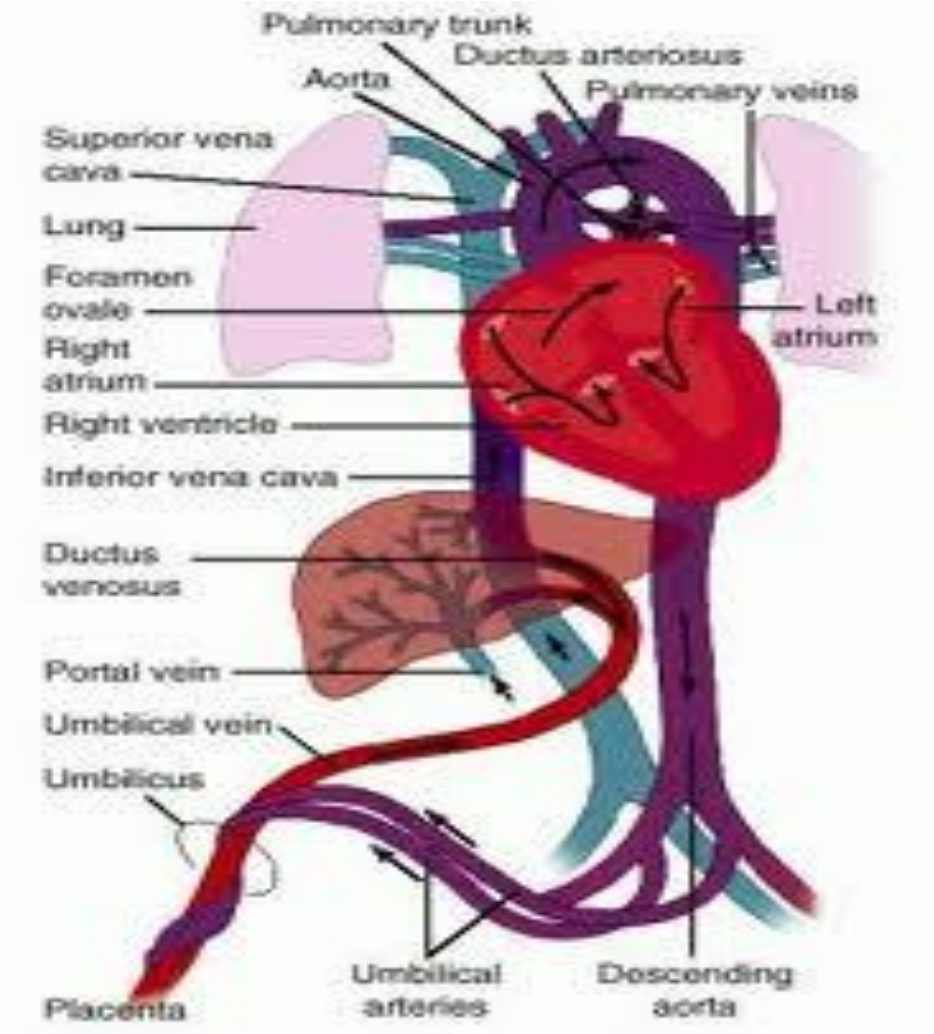
Nutritional Deficiency – Famine, Inflammatory bowel diseases

FETAL AND MATERNAL BLOOD CIRCULATION SYSTEMS

The placental circulation brings into close relationship two circulation systems : The maternal and the fetal. The supply of blood to the placenta is influenced by various factors, especially the arterial blood pressure, uterine contractions, tobacco abuse, medication and hormones. Placental blood flow is increased at term and accounts to 500 ml / min (80% of uterine perfusion).

Fetal circulation system

The villous capillaries are branches of umbilical vessels. Fetal blood comes via the two umbilical arteries and leaves the placenta through a single vein. Their supply amounts to approximately 40% of the fetal heart blood volume per minute.

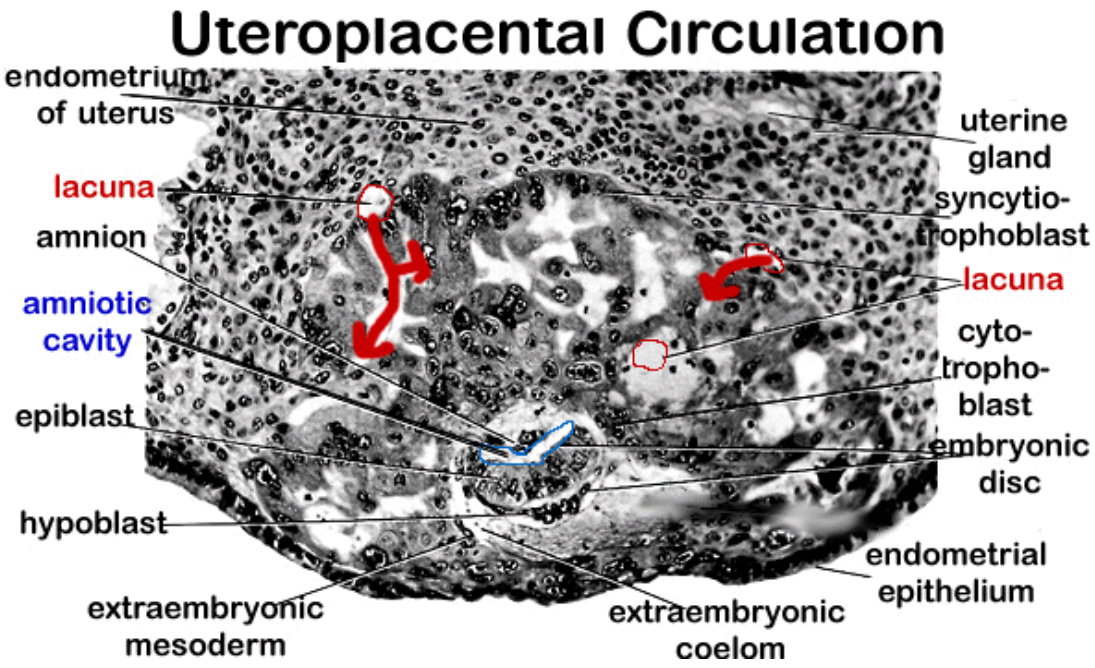


The blood pressure in the arteria umbilicalis amounts to 50 mmHg and blood flows through finer vessels that cross the chorionic plate to the capillaries in the villi where the arterial blood pressure falls to 30 mm Hg. In the umbilical vein, the pressure is 20mm Hg. The pressure in the fetal vessels and their villous branches always lie over that of intervillous space. This protects the fetal vessels from collapse.

Maternal Circulation system : Utero placental circulation :

During pregnancy, the uterine circulation constantly adapts in order to be adequate for the growing metabolic needs of the embryo via the spiral arteries that come from the uterine arteries. Maternal blood gets into the intervillous space in a region delimited by anchoring villi. Subsequently the blood leaves the intervillous space via the uterine veins that are arranged in the periphery of intervillous space.

The flow of placental blood amounts to 600 cm3/mt and the pressure in the spiral arteries to 70mmHg in the intervillous space. The pressure falls to only 10mmHg. The blood in the intervillous space is exchanged 2-3 times per minute.



Intervillous haemodynamics :

Volume of blood in mature placenta : 500 ml

Volume of blood in intervillous space : 150 ml

Blood flow in intervillous space : 500 – 600 ml / min

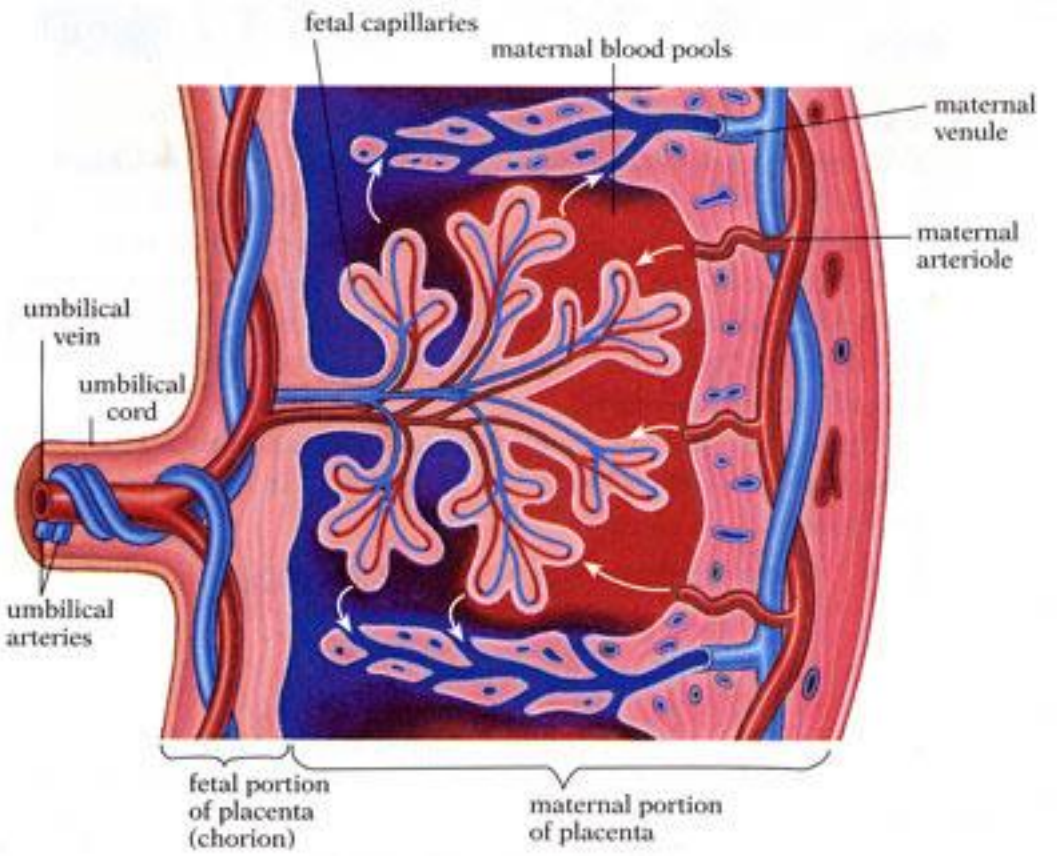
Pressure in intervillous space

During uterine contraction : 30 – 50 mm Hg

During uterine relaxation : 10 – 15 mm Hg

Pressure in uterine artery : 70 – 80 mmHg

Pressure in draining uterine vein : 8 mm Hg



About 120 – 200 spiral arteries open into the intervillous space by piercing the basal plate randomly at numerous sites. Normally there is cytotrophoblastic invasion of spiral arteries initially upto the intradecidual portion within 12 weeks of pregnancy. The musculo elastic media is destroyed and replaced by fibrinoid material. There is a secondary invasion of trophoblast between 12-16 weeks extending upto radial arteries within the myometrium. The spiral arteries are converted into large bore uteroplacental arteries. The net effect is funnelling of the arteries which reduces the pressure of blood to 70-80mm Hg before it reaches the intervillous space. It thus increases the blood flow.

The venous blood of the intervillous space drains through the uterine veins which pierce the basal plate randomly like the arteries. This concept of uteroplacental circulation is based on the studies of Ramsay and Coworkers (1963).

REGULATION OF FETAL GROWTH

Defining disorders of growth requires relating a given achieved growth to an expected growth. The primary interest in assessing fetal growth is to avoid complication associated with a fetus poorly grown due to uteroplacental insufficiency. The most

important consequence of fetal comprimise is perinatal death, principally antepartum still birth.

Factors regulating fetal growth

1. Endocrine regulation of fetal growth
2. Placental regulation of fetal growth
3. Genomic imprinting and fetal growth

Endocrine regulation of fetal growth

Fetal growth is critically regulated by Insulin like growth factors (IGFs). IGFs are of 2 types IGF -1 and IGF 2. The effects of IGFs are influenced by six distinct IGF binding proteins (IGFBP). A number of IGFBP proteases exist such as pregnancy associated plasma protein– A (PAPP –A), a protease for IGFBP-4 and IGFBP-5. Many associations have been described between cord blood, amniotic fluid and maternal serum levels of components of IGF system and fetal growth.

Placental regulation of fetal growth

The placenta is clearly crucial for fetal growth as it provides all the substrates for fetal growth and performs gaseous exchange in fetal life. Some of the associations between IGF system proteins and eventual birth weight are placentally derived components, such as

PAPP-A, as IGFs are also important in controlling placentation. Placental function tests demonstrate association with eventual fetal growth. Many complications of pregnancy associated with poor placental function may be due to failure of the ‘second wave’ of trophoblast invasion in the second trimester. There are associations between both the size of fetus in the first trimester of pregnancy and maternal levels of PAPP-A and the eventual birth weight of the baby.

Genomic imprinting and fetal growth

Key genes of IGF system are imprinted. Genomic imprinting is the selective inactivation of a gene in the conceptus in relation to maternal or paternal copy. Genomic imprinting is a feature of placental mammals. In fetal life this is manifested in the control of fetal growth. The key role of placental IGF system is the fact that IGF-2– a stimulator of placental invasion is paternally imprinted and type-2, IGF receptor which degrades IGF–II is maternally imprinted. Aberrant expression of imprinted genes may lead to fetal over growth or intrauterine growth restriction.

Pathophysiology of IUGR

Compared with an average for gestational age fetus, the IUGR fetus has altered body composition (including decreased body fat, total protein, whole body DNA and RNA, glycogen and free fatty acids) altered distribution of weight among organs and altered body proportions. Approximately, 20% of IUGR infants are symmetrically small with a relative proportionate decrease in many organ weights. Eighty percent are asymmetrically small, with relative sparing of brain weight, compared to liver or thymus.

In asymmetric IUGR, brain weight is decreased only slightly compared with that of AGA controls, due to decrease in brain cell size. Cerebral abnormalities include decreased myelination, decreased utilization of metabolic substrates other than glucose and altered protein synthesis. Deprivation in early pregnancy is associated with less cerebral sparing and diffusely slowed brain growth.

Symmetric IUGR infants have proportionately small brains due to decreased number of brain cells. The cause is more often a genetic disorder or infection leading to early severe nutritional deprivation. The thymus is small with an average decrease of 25%.

The decrease may explain the decreased cellular immunity seen in IUGR infants.

Liver is frequently affected, atleast partly because of diminished glycogen deposits. The liver also may have functional metabolic abnormalities manifested by cord blood and neonatal serum chemistries. Such abnormalities reflect the underlying cause for decreased size.

Blood flow to the lungs may be decreased lessening the pulmonary contribution to amniotic fluid volume responsible for oligohydramnios. Decreased pulmonary blood flow is associated with accelerated functional pulmonary maturity.

Renal blood flow is reduced in asymmetric IUGR pregnancies. Diminished glomerular filtration rate may contribute to oligohydramnios.

MATERNAL CONTRIBUTION TO ABERRANT FETAL GROWTH PHYSICAL ENVIRONMENT

Certain normal mothers are prone to repeated delivery of SGA infants, the recurrence rate may be 25% to 50%. These women may themselves were SGA, the possibility of non genetic inter generational transmission of a physical regulator of fetal growth.

These women exert a restraint on fetal growth by unknown regulator related to their own stature, previous nutritional status or uterine capacity.

Another risk for IUGR is maternal failure to expand their plasma volume during pregnancy leading to reduced placental weight and hematocrit.

Maternal genetic factors have a major effect on fetal growth related in part to uteroplacental function. Paternal factors have less effect on fetal growth. The uterine capacity may itself place a constraint on optimal fetal growth.

Maternal nutrition

Prepregnancy weight and pregnancy weight gain are two important independent variables that affect fetal growth. Underweight mother and those affected with malnutrition deliver infants with diminished birth weight. Weight gain during pregnancy in non obese patients correlates significantly with fetal birth weight. Poor weight gain as early as 16 weeks gestation may predict low birth weight.

Calculating the pregravid body mass index (BMI)

$$\text{BMI} = \frac{\text{Prepregnancy weight (kg)} \times 100}{\text{Height}^2 \text{ (m)}}$$

It helps the clinician to determine the target for pregnancy weight gain, which may reduce the risk of IUGR. An underweight women (BMI<18.5) may require a pregnancy weight gain of 12.5 to 18 kgs, a normal weight woman (BMI -18.5 to 24.9) need a weight gain of 11.5 to 16 kgs and a overweight woman (BMI- 25 to 29.9) require a weight gain of 7 to 11.5 kgs, whereas obese women BMI (> 30) may need a weight gain of only 6 kgs.

The effects of maternal nutritional status on fetal growth are minimal during the first trimester of pregnancy. As fetal growth accelerates, the requirements for fetal growth increases and may not be sufficiently provided by an inadequate maternal diet.

Decreased caloric uptake below critical caloric needs may result in diminished fetal growth. A threshold of 1500 kcal/day augmented fetal weight when the mother was in positive caloric balance.

Certain metabolic aberrations are associated with suboptimal growth. Mothers with excessively low fasting blood glucose values and those whose blood glucose levels are not sufficiently elevated after an OGTT are at risk of delivering an SGA infant.

Chronic diseases

Chronic maternal hypertension caused by primary renal parenchymal diseases (nephritis) or extrinsic parenchymal disorders such as essential hypertension alters fetal growth and well being. Pregnancy induced hypertension may affect uteroplacental perfusion and fetal growth as determined by Doppler flow velocity waveforms of uterine artery. Preeclampsia is characterized by defective endovascular trophoblastic invasion, reduced perfusion of the intervillous space, necrotizing atherosis and decreased trophoblastic invasion of decidual spiral arteries. In pregnancies complicated by eclampsia, fetal growth deviates from expected norm from 32 weeks onwards.

Diminished fetal weight gain also results from maternal hypoxia due to severe cyanotic congenital heart disease, sickle cell anaemia and diminished environmental oxygen saturation present at high altitude.

Drugs

Drugs causing IUGR may be due to direct cellular cytotoxicity or by reducing maternal appetite [ex. Amphetamines, Antimetabolites, cocaine, Bromides, Ethanol, heroin etc)

Cigarette smoking during pregnancy reduces eventual fetal birth weight and related directly to number of cigarettes smoked. Birth weight at term is reduced to an average of 170gms if >10 cigarettes used per day and use of more than 15 per day may reduce weight by 300 gms.

Nicotine and subsequent catecholamine release may produce uterine vasoconstriction and fetal hypoxia. Carbon monoxide and cyanide may cause direct effect.

PLACENTAL DETERMINANTS

Optimal fetal growth depends on efficient function of placenta as both a nutrient supply line and an organ of gaseous exchange. Placental functional integrity requires additional energy production because placental oxidative metabolism may equal that of fetus. Large energy requirements is essential to maintain fetal growth promoting roles which includes active transport of aminoacids,

synthesis of protein and steroid hormones and support of placental maturation and growth.

Placental growth parallels to that of fetus, towards term there is a decline in the rate of placental weight gain than in the rate of weight gain by fetus. The placental villous surface area continues to increase with advancing gestational age, simultaneously the syncytiotrophoblast layer continues to thin and vascularisation of the terminal villi continues to improve. Functionally, urea clearance is enhanced towards term suggesting that permeability and diffusing distance improve as placenta approaches towards term.

Birth weight has been correlated to placental weight and villous surface area suggesting macroscopic and microscopic events are related to optimal placental function. Uterine blood flow and thus placental oxygen or nutrient transfer may be reduced if maternal blood volume contracts. Failure to expand plasma volume, which normally occurs in later half of gestation has been associated with IUGR. These high risk women may be identified through an elevated hemoglobin level.

When placental insufficiency occurs, there may be a functional failure of placenta as a respiratory or nutritive organ or both.

Placental insufficiency associated with maternal nutritional deficiency has more than one effect on fetal growth. In addition to diminished fetal substrate provision, placental metabolism will be altered directly. Diminished placental growth will adversely affect total nutrient transfer, where as reduced placental production of chorionic somato mammotropin will attenuate maternal mobilization of fuels to the fetus. Reduced placental energy production and protein synthesis limits active transport of aminoacids and facilitate transport of glucose.

FETAL DETERMINANTS

Optimal fetal growth depends on adequate provision of substrates, their effective placental transfer and inherited regulatory factors within fetal genotype.

Factors affecting fetal growth

A. Chromosome disorders associated with IUGR
    1. Trisomy 13, 18, 21
    2. 4p syndrome
    3. 5p syndrome
    4. Triploidy, XO

B. Metabolic disorders
    1. Agenesis of pancreas
    2. Congenital absence of Islets of langerhans

3. Congenital lipodystrophy
4. Maternal renal insufficiency

C. Syndromes associated with IUGR
1. Bloom syndrome
2. Dwarfism
3. Meckel – Gruber syndrome
4. Mobius syndrome

D. Congenital infections associated with IUGR
1. Rubella
2. Cytomegalovirus
3. Toxoplasmosis
4. Malaria, syphilis

DIAGNOSIS

History

Patients with significant medical or obstetric history such as chronic hypertension, severe toxaemia of pregnancy, chronic renal disease, twins and advanced insulin dependent diabetes are at high risk of having an IUGR fetus. The obstetric history of prior delivery of IUGR baby is also important. Other risk factors are BMI < 19 and maternal smoking, congenital uterine anomalies.

Clinical assessment

A. Weight gain : Relatively insensitive sign of inadequate fetal growth. Normal weight gain in pregnancy is around 10-12 kgs. Weight gain below 6 kg should give a suspicion of IUGR.

B. Symphysiofundal Height

Maternal uterine fundus is objectively measured and charted during each antenatal visit. After 20 weeks gestation, the normal symphysial fundal height in centimeters approximates the number of weeks of gestation, after appropriate allowances for maternal height and fetal gestation. The sensitivity ranges from 60% - 85% and positive predictive value are 20% - 80%.

Biochemical

Four hormone or protein markers measured in maternal sera early in second trimester are associated with IUGR. These include estriol, human placental lactogen, HCG and alpha fetoprotein. Clinically maternal serum alpha fetoprotein is the most useful marker of abnormal placentation.

Ultrasound assessment

USG biometry is the diagnostic tool of choice for the documentation of fetal growth disorders. Accurate assessment of gestational age is a necessary first step so that percentile ranks of absolute measurements can be derived. Because fetal growth restriction has many underlying etiologies that affect the timing of onset and fetal features, no single sonographic method is adequate for diagnosis.

DIRECT MEASUREMENTS

Biparietal Diameter :

It is a poor tool for detection of IUGR. The physiologic variation with advancing gestation is high, cranial growth delay as a result of insufficient nutrition is relatively late and the shape of the cranium is readily altered by external forces. (eg. Oligohydramnios, breech presentation)

Head circumference :

It is better than BPD in predicting IUGR. It is not subjected to variability as is BPD. The cephalic index, which is the ratio of BPD to occipitofrontal diameter is age dependent and helps in identifying dolicocephaly and brachycephaly.

Transverse Cerebellar diameter[TCD]:

Upto 25 weeks, the measurement of TCD in cm equals gestational age in weeks. Serial measurements have more predictive value than a single measurement.

Abdominal circumference (AC) :

AC and fetal weight are the most accurate ultrasound parameters for diagnosis of IUGR. AC has the highest sensitivity and greatest negative predictive value for sonographic diagnosis of IUGR. An increase in fetal AC of less than 10mm in 14 days has a sensitivity of 85% and specificity of 74% for identification of IUGR. Fetal weight can be calculated by a variety of formula (Hadloc, Ott, Shepherd)

MEASUREMENT RATIOS

Head to Abdomen Ratio HC / AC :

In a normally growing fetus, the HC / AC ratio exceeds 1.0 before 32 weeks. It is approximately 1.0 at 32-34 weeks. After 34 weeks, it falls below 1.0. An HC / AC ratio > 2 SD above the mean is predictive of IUGR. Serial measurement of AC and estimation of fetal weight are more diagnostic of fetal growth restriction.

Femur length to Abdomen circumference Ratio :

FL / AC ratio is gestational age independent. Normal value is 22 at all gestational ages from 21 weeks till term. FL / AC ratio greater than 23.5 suggests IUGR.

Amniotic fluid volume :

Type 2 IUGR is associated with oligohydramnios. AFI is determined by adding the depths of largest vertical pockets in the 4 quadrants of the uterus.

Incidence of IUGR in Oligohydramnios

Vertical pocket	Incidence of IUGR
> 2cm	6%
1-2 cm	20%
< 1 cm	39%

Placental dysfunction and fetal hypoxemia may result in decreased perfusion of fetal kidneys and subsequent oliguria and oligohydramnios.

Fetal Ponderal Index

Degree of fetal wasting is judged by fetal ponderal index. It is estimated by dividing the estimated fetal weight by third power of femur length (weight / length3). PI below 10^{th} percentile is taken as

IUGR. Its normal value is 8.325 ± 2.5. An FPI of 7.0 or less is considered abnormal.

Doppler Ultrasonography

The most widely used arterial indices are pulsatility index, systolic to diastolic ratio and resistance index.

$$\text{Pulsatility index} : \frac{\text{Peak Systolic- end diastolic peak velocity}}{\text{Time averaged maximum velocity}}$$

$$\text{Resistance Index RI} : \frac{\text{Peak Systolic - end diastolic peak velocity}}{\text{Systolic peak velocity}}$$

$$\text{Systolic to Diastolic Ratio} : \frac{\text{Systolic Peak velocity}}{\text{Diastolic peak velocity}}$$

As the vascular impedance of placenta increases, fetal protective mechanism are triggered which are reflected in Doppler studies. The temporal sequence of Doppler changes are : Amniotic fluid index and umbilical artery pulsatility index are the first to become abnormal followed by changes in MCA velocimetry, aorta Doppler study, ductus venosus wave form and inferior venacava Doppler.

Umbilical Artery :

In IUGR, there is a chronological process characterized by increased umbilical artery resistance S/D ratio, absent end diastolic

flow, reverse end diastolic flow. Perinatal mortality increases significantly in fetuses with absent end diastolic flow (9-41%) and reversed end diastolic flow (33-73%) in the umbilical artery.

Middle Cereberal Artery :

Increased resistance to blood flow in the placenta results in a redistribution of the cardiac output to favour cardiac and cerebral circulations. This results in an increased flow in the diastolic phase with reduced S/D ratio. The cerebral placental ratio (ratio between MCA PI and umbilical artery PI) is considered to be more sensitive predictor to detect redistribution of blood flow.

Ductus venosus :

In IUGR, when circulatory compensation of the fetus fails, the DV wave form shows absent or reverse blood flow during atrial contractions. Pulsation of umbilical vein may be seen. The perinatal mortality ranges from 63 – 100%, hence fetus should be delivered before the development of absent or reversed diastolic flow.

PLACENTA

Placenta is a temporary organ for the development of embryo and fetus. The human placenta is discoid, hemochorial, deciduate.

Placenta is developed from 2 sources.

1. Fetal - chorion frondosum
2. Maternal - Decidua basalis

It begins at 6^{th} week and completed by 12^{th} week.

Term placenta

It is a circular disc with diameter of 15 – 20 cm and thickness of 2.5 cm at its centre. It is spongy and weigh around 500 gm and the placentary index is 1 : 6 at term. At term four – fifth of placenta is of fetal origin. The maternal portion amounts to less than $1/5^{th}$ of placenta constituting only the decidua basalis and blood in the intervillous space.

Villous structure of placenta

These arise from the chorionic plate and extends to the basal plate. From the main stem villi – primary, secondary, tertiary villous are formed. Functional unit of placenta is fetal cotyledon or placentome, derived from a major primary stem villous. Functional subunit of placenta is a lobule, derived from tertiary stem villi. The

total villous surface area for exchange varies between 4-14 square meters. The villi functions to anchor the placenta to the decidua and majority are free within the intervillous space and are called nutritive villi.

Functions of Placenta

1. Transfer of nutrients and waste products: Between mother and the fetus by simple diffusion, facilitated diffusion, active transfer and endocytosis / exocytosis.
2. Metabolic functions : Metabolises the hormones and enzymes necessary to maintain pregnancy.
3. Respiratory function : Intake of O2 and output of CO2 takes place by simple diffusion across fetal membrane. The oxygen supply to the fetus is at the rate of 8 ml / kg / min and achieved with a cord blood flow of 165 – 330 ml / min.
4. Excretory function : Waste products from the fetus such as urea, uric acid, creatinine are excreted by simple diffusion.
5. Nutritive function :

   Glucose - Facilitated diffusion

   Lipids - Denovo synthesis and direct transfer

   Aminoacids - Active transport

Water and electrolytes - Simple diffusion

[Na+, K+, Cl-]

Ca2+, P, Fe - Active transport

6. Enzymatic function:

Diamine oxidase – inactivates circulatory pressure amines

Oxytocinase - Neutralise the oxytocin

Phospholipase A2 → Synthesise arachidonic acid

7. Barrier function:

Protective barrier to the fetus against noxious agents such as virus, protozoa and certain drugs

8. Immunological function :

Placenta probably offers immunologic protection against rejection of fetal allograft.

RATIONALE FOR PLACENTAL EXAMINATION

Gross placental examination is important for 2 reasons.

1. Placental gross abnormalities may provide clinicopathologic correlations with obstetric events [ex : very small placental size and infarct strongly suggest chronic placental ischaemia, while ruptured membranous vessels may explain fetal death or anaemia].

2. To identify regions that should be studied further by histology.

A recent analysis of obstetric malpractice claims concluded that many more neurologically impaired infant claims could be successfully defended if placenta specimens were available for evaluation at the time a claim is made.

Gross Examination of Placenta

General Appearance

Shape : Variations include bilobation, Trilobation, Accessory / Succenturiate lobation, placenta membranacea.

Although the collaborative perinatal study suggests that some of these abnormal placental shapes may be associated with adverse outcomes little literature exists in this area.

Weight :

Abnormally small placenta are most commonly associated with chronic uteroplacental hypoperfusion and fetal growth retardation. Exclusively heavy placentas may signify diabetes, severe villous edema, fetal hydrops and congenital syphilis. Placental weights above the 90^{th} or below the 10^{th} percentile for gestational age should be noted in pathology report.

Conditions associated with small placentas (< 10^{th} percentile)	Conditions associated with large placentas (>90^{th} percentile)
Chronic placental underperfusion Fetal growth retardation Chromosomal disorders Congenital malformations Possible neurologic outcome such as cerebral palsy	Maternal diabetes Fetal hydrops Congenital syphilis Villous edema Chorangiosis Beckwith Wiedeman syndrome

Colour:

Dull, white opaque appearance in acute chorioamnionitis.

Brown discoloration of membrane and chorionic plate – Hemosiderin deposition secondary to chronic abruptio placenta.

Slimy green appearance – meconium staining.

UMBILICAL CORD AND MEMBRANE

Umbilical cord

1. Insertion : Marginal insertion in 5% of placenta.
2. Distribution of vessels : Velamentous insertion - 1%.
3. Twist : Untwisted cord suggest prolonged fetal inactivity

(muscular disorder, fetal entrapment)

4. Length : Short cord (< 40 cm)– Prolonged fetal inactivity.

Excessively long cord-fetal death.

5. Color : Yellow green – meconium exposure .

Diffuse brown red - fetal retention after death.

6. Knots : True knots if tight and constricting - fetal death.

7. Vessel number : Single umbilical artery (1%) - numerous fetal malformations, fetal aneuploidy and fetal death.

MEMBRANES

1. Distribution : Circummarginate / circumvallate.
2. Integrity : Amniotic band syndrome - Asymmetric fetal abnormalities
3. Opacity and color : Greenish color – Meconium staining.

Red brown – Hemosiderin.

4. Odour : Foul odour reflect infection.

PLACENTA OF IUGR FETUSES

Placental Size

With the introduction of prenatal ultrasound examination, it has been reported that unduly small placental volume during the

second trimester is strongly associated with subsequent low birth weight. (Thame et al 2001, 2004).

The reduced placental size is due to reduced uteroplacental blood flow due to incomplete or insufficient trophoblastic invasion of the spiral arteries in the placental bed. When placentation is abnormal, trophoblastic invasion is largely confined to the decidual layer with absent or incomplete changes in the myometrial portion of spiral and radial arteries causing increased vascular resistance and decreased blood flow to the intervillous space, restricting the maternal capacity to provide oxygen and nutrients to the fetus.

Immuno Histochemical markers :

Placental apoptosis does appear increased in pregnancies affected by fetal growth restriction (Ishihara et al 2002) and associated with decreased expression of inhibitors of apoptosis. Cellular proliferation rate in these placentas using immunohistochemical technique have reported both normal and reduced proliferation (Chen et al 2002).

Expression of VEGF (Vascular Endothelial growth factor) and its receptor in placentas complicated by fetal growth restriction has been reported as both increased (Helske et al 2001) and unchanged

(Tse et al 2001). Endothelin I immuno reactivity appears reduced in the capillary endothelial cells of villi from growth restricted pregnancies.

The proto oncogenes c-jun and c-fos m-RNA expression were significantly over expressed in IUGR fetus. Conflicting findings exist about the expression of IGF and its receptors. Fetal growth restriction is associated with reduced concentration of both placental and cord blood leptin, decreased placental Interleukin – 10 (IL-10) m- RNA expression, whilst (IL-8) m – RNA expression is increased.

Production of matrix metallo proteinases and placental growth hormone may be reduced in pregnancies complicated by inadequate fetal growth whereas expression of TGF – B is relatively unaffected.

GROSS ABNORMALITIES

Gross variations in the shape of placenta, circumvallate placenta, reduced placental size and reduced placental weight and a dull white opaque appearance due to chorioamnionitis or meconium staining may be found in placenta of IUGR.

Maternal floor Infarction :

Infarcts are best recognized by their gritter, granular consistency, which is related to villous composition. Infarcts are

commonly located closed to the maternal fetal interface, reflecting their pathogenesis in diseased maternal spiral arterioles. Recent infarcts are dark red, older infarcts are brown red to tan to yellow white colour.

Extensive Perivillous Fibrin Deposition :

Placental cut surface shows marbling of the placental parenchyma by tan white fibrinous material in a nodular to diffuse pattern.

Thrombosis of Fetal arteries :

Fetal thrombosis is found in approximately 40% of placentas of fetus with IUGR. Several distinctive pattern of placental disease indicative of fetal thrombosis may be seen including i) Thrombi in large fetal vessels 2) Clusters of avascular terminal villi.

Hemorrhagic endovasculitis :

Thrombi may be grossly visualized as dilated dark red vessels (recent) or shrunken tan white sometimes calcified vessels (remote).

Chorangiomas :

Chorangiomas are located adjacent to the fetal surface of placenta. Usually contiguous with the chorionic plate or large stem villi.

Gross placental abnormalities associated with abnormal childhood mental, neurological, psychological outcome

Placental abnormality	**Abnormal outcome**
Short umbilical artery	MR, Neuro, CP
Single umbilical artery	MR, Neuro
Velamentous cord insertion	Psych
Green coloured umb. Cord (meconium)	Psych
Long umbilical cord	Psych
Opaque fetal surface(chorioamnionitis)	MR,neuro, Sz
Circumvallate membrane insertion	Neuro
Meconium stained amniotic fluid	CP, MR, Sz
Absent Subchorionic fibrin	MR, neuro, CP
Succenturiate lobe	MR, Sz
Maternal floor infarct	MR, Neuro
Bipartite / Tripartite shape	MR, Neuro, Psych
Diffuse chorionic fibrin	Psych, Neuro

MR - Mental retardation

Neuro - various neurological disorders – Abnormal speech, poor motor co-ordination

CP - Quadriplegic, paraplegic, hemiplegic cerebral palsy

Sz - Seizures

Psych : Behaviour disturbances, attention deficit disorder

(adapted from Narye)

Histological abnormalities :

Placental pathology in IUGR

1. Chronic placental Ischaemia (30%)
2. Chronic villitis
   - Infectious villitis (TORCH)
   - Non specific villitis
   - Massive chronic intervillositis
3. Fetal vasculopathy (40%)
   - Fetal thrombosis
   - Hemorrhagic endovasculitis
   - Diffuse villous fibrosis
4. Increased perivillous fibrin
5. Vascular malformation (mesenchymal dysplasia)

The fetal side of the placenta may show changes secondary to or independent of the alterations in the maternal side. The most common lesions found on the fetal side of the placenta are increased number of syncytial knots, obliteration of arteries in the tertiary stem villi, reduction in the vascularity of terminal villi and stromal fibrosis.

Thrombosis in maternal side of the placenta coexists with alteration in uteroplacental blood flow, clotting in the spiral arteries or the intervillous space results in placental infarcts that reduce the number of functioning villi and affects the supply of oxygen and nutrients to the fetus.

In massive perivillous fibrin deposition the intervillous space is occupied by fibrin and villi embedded in the fibrinous mass are non functional. This lesion strongly suggest the possibility of maternal thrombophilia.

Maternal floor infarction is characterized by massive deposition of fibrin in the maternal floor of the placenta encasing the contiguous villi that become atrophic / necrotic. It is associated with IUGR in > 50% cases. This condition frequently reoccurs in successive pregnancies.

Lymphocytic and histiocytic infiltration of the villi are markers for chronic villitis, a nonspecific lesion frequently associated with vascular lesions in the maternal or fetal side of the placenta. Chronic villitis occurs in approximately 8% in normal pregnancies but incidence increases 3-4 fold in cases of IUGR.

Hemorrhagic endovasculitis is associated with poor pregnancy outcome and histologically characterized by the presence of numerous extravascular erythrocytes infiltrating the villi. Both hemorrhagic endovasculitis and chronic villitis are frequently present in placentas from women with preeclampsia.

Clotting and thrombosis may be found in fetal side of the placental circulation. Fetal thrombotic vasculopathy occur simultaneously with infarcts or decidual vasculopathy in the maternal side of the placenta. Fetal vasculopathy has a strong association with poor pregnancy outcome. There is an association between the placental lesion and thromboembolic lesions in fetal brain.

Subclassification of Placental pathologies in IUGR

Subclassification	Placental Findings
Vascular or Ischaemic pathology	Congested villi Villous hemorrhage (Intravillous) Villous infarction (gross and microscopic) Intervillous thrombosis Decidual vasculopathy Decidual hemorrhage Abruption Fetal surface vessel / umbilical vessel thrombosis
Inflammatory pathology	Villitis
Villous maturation disorder	Delayed / Advanced Dysmaturity / Variable Chorangiosis
Other isolated abnormalities	Isolated membrane abnormality Amnion nodosum / meconium deposition Isolated cord edema / isolated villous edema Mild perivillous fibrin deposition

COMPLICATIONS OF IUGR:

•Fetal complications ➡Stillbirth, hypoxia/acidosis, malformations

•Neonatal complications ➡Hypoglycemia, hypocalcemia,

Hypoxia & acidosis, hypothermia, meconium aspiration ,

Polycythemia, hyperbilirubinemia, sepsis, low APGAR score

congenital malformations, apneic spells, intubation

sudden infant death syndrome

•Long term complications ➡Lower IQ, learning & behavior problems, major neurological handicap ➡seizures, cerebral Palsy, mental retardation.

•Perinatal mortalility 1.5-2 times increased OR.

Placental pathology and Perinatal outcome :

Abnormal uteroplacental vasculature and chronic uteroplacental insufficiency, coagulation related pathology in the uteroplacental, intervillous and/or fetoplacental vasculature and chronic inflammatory lesions may be the primary disease process related to the placental pathology of IUGR. The incidence of neurologic morbidities in IUGR infants was 1-7 fold higher than normal cases. Although the cause of IUGR pregnancies is heterogenous, careful clinicopathologic correlations in individual cases are necessary in the interpretation of placental lesions of IUGR and the total burden of several placental lesions may be more important than a single histologic feature. Total number of placental lesions >3 was associated with an increased risk for IUGR.

MATERIALS AND METHODS

Study Design :

Analytical study

Source of Data :

The study was carried out in the Department of Obstetrics and Gynaecology, GRH, Madurai. 100 placentas of IUGR babies were collected during the study period from October 2010 – November 2011.

Inclusion Criteria :

Placentas of pregnant women who delivered term IUGR babies. (Birth weight less than10th percentile according to standard normal curves).

Exclusion Criteria :

1. Known congenital anomaly in fetus
2. Twin pregnancies
3. Prematurity
4. Unreliable LMP without first trimester scan

Method of study : In this study, mothers who delivered IUGR babies were enrolled as cases. For each case details as mentioned in the structured proforma were collected after delivery.

Ultrasound parameters including fetal biometry, estimated fetal weight, amniotic fluid index and Doppler USG of the umbilical artery were noted.

Immediately after delivery, the newborn is weighed and the birth weight percentiles were determined by previously published normal curves by Alexander GR in 1996. The placentas were weighed and macroscopic examination done which includes the placental diameter, thickness, colour, calcification and other abnormalities noted.

The placentas are sent to Pathology department for histopathological examination by a senior pathologist.

Placental histologic data includes decidual vasculopathy, fetal thrombotic arteriopathy, chorangiosis, acute inflammation, chronic villitis and intervillous thrombosis.

The frequency and cumulative number of placental abnormalities in IUGR babies were determined and the relationship to perinatal outcome was determined in terms of fetal weight, Apgar scores and perinatal mortality.

RESULTS AND OBSERVATIONS

Total of 100 cases of IUGR were included in the study. The observations and results of the study are presented in the following pages.

Table – 1

Age distribution in the study (years)

Age	No.of cases	Percentage
$\leq$ 20	15	15
21 – 30	80	80
$\geq$ 31	5	5
Total	100	100

80% of patients are in the age group 21-30 years, and only 5% above 31 years.

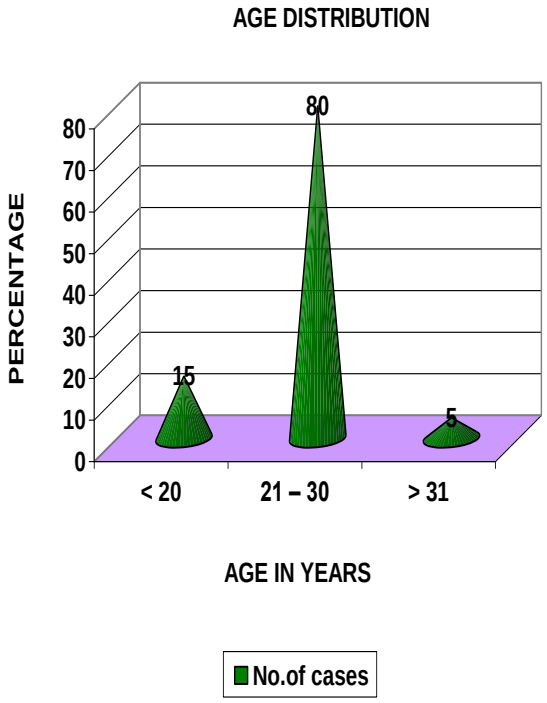

AGE DISTRIBUTION
PERCENTAGE
80
70
60
50
40
30
20
10
0
80
15
5
< 20
21 – 30
> 31
AGE IN YEARS
No.of cases

Table – 2

Parity Distribution

Gravida	No.of cases	Percentage
1	48	48
2	31	31
3	17	17
4 and above	4	4
Total	100	100

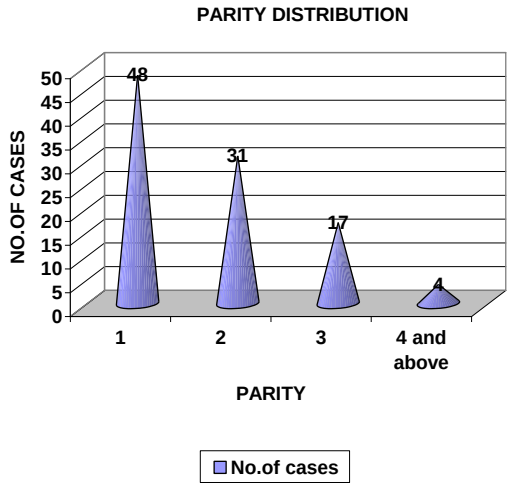
48% of them were primigravida.

Table – 3

Distribution based on Socio economic status

Socio economic status	No.of cases	Percentage
V	58	58
IV	30	30
III	8	8
II	4	4
I	0	0
Total	100	100

58% of patients belong to class V socioeconomic status.


PARITY DISTRIBUTION
NO.OF CASES
50
45
40
35
30
25
20
15
10
5
0
48
31
17
4
1
2
3
4 and above
PARITY
No.of cases

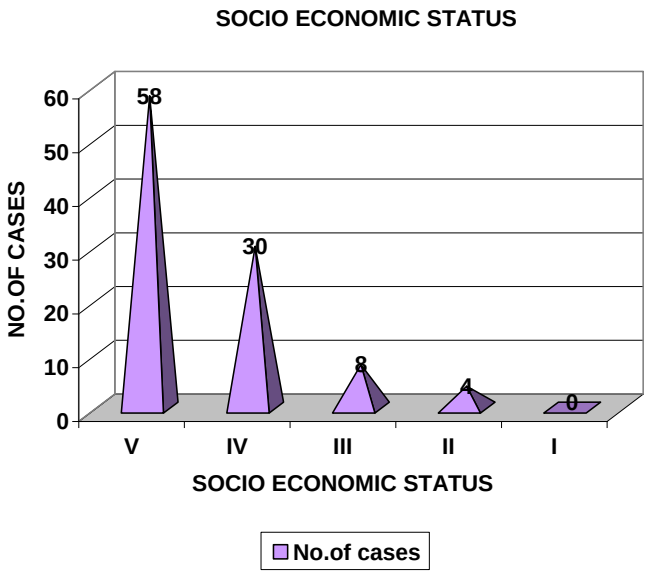

SOCIO ECONOMIC STATUS
NO.OF CASES
60
50
40
30
20
10
0
58
30
8
4
0
V
IV
III
II
I
SOCIO ECONOMIC STATUS
No.of cases

Table – 4

Distribution of cases based on Etiology

Etiology	No.of cases	Percentage
Idiopathic	45	45
PIH	28	28
Anemia	14	14
Heart Disease	4	4
Placenta previa	2	2
Chronic maternal disease	4	4
Miscellaneous	3	3
Total	100	100

45% of cases are due to unknown etiology, followed by pre eclampsia 28%, 14% due to anaemia, 4% due to heart disease.

Chronic maternal disorders include 2 cases of chronic hypertension,1 case of chronic nephritis,1 case of panniculitis.

The miscellaneous group comprised the following etiologies i)connective tissue disorders (1) ii) Inflammatory bowel disease (1), iii) Bronchial asthma (1).

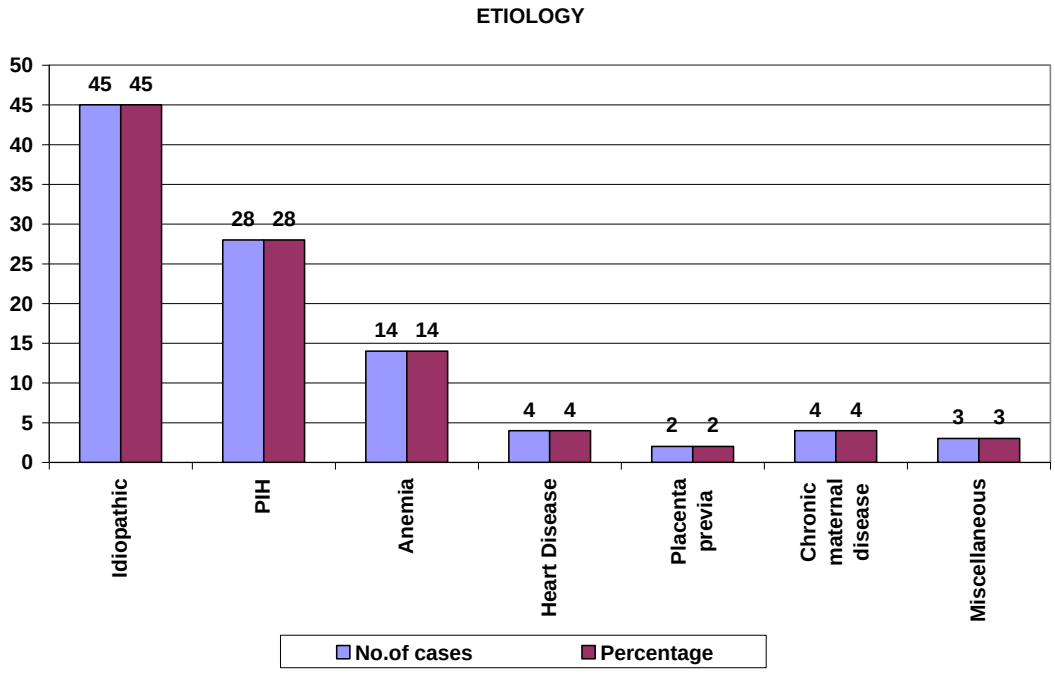

ETIOLOGY
50
45
40
35
30
25
20
15
10
5
0
45 45
28 28
14 14
4 4
2 2
4 4
3 3
Idiopathic
PIH
Anemia
Heart Disease
Placenta previa
Chronic maternal disease
Miscellaneous
No.of cases
Percentage

Table – 5

Based on Pregnancy weight gain

Weight gain	No.of cases	Percentage
< 5 kg	1	1
6 – 10 kg	87	87
> 11 kg	12	12
Total	100	100

About 87% of patients had weight gain of 6-10 kgs, only 12% had weight gain > 11 kgs.

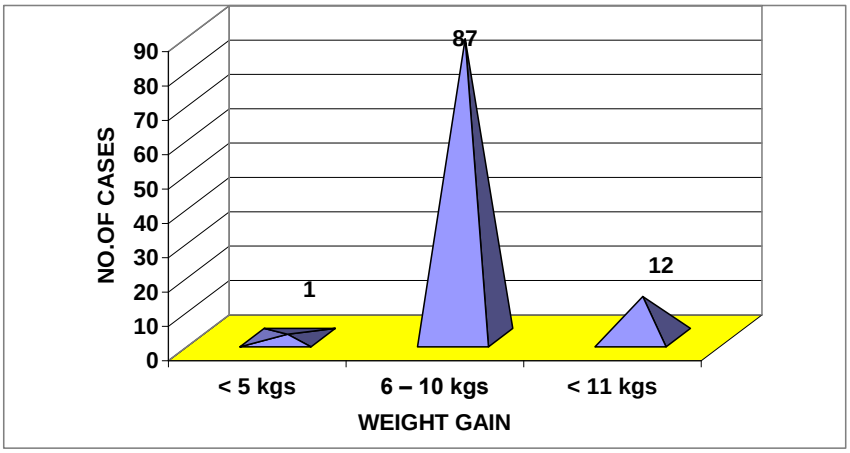
Table – 6

Distribution of cases based on Amniotic fluid Index

AFI	No.of cases	Percentage
< 5	51	51
5 – 10	36	36
11 – 15	13	13
Total	100	100

About 51% had oligohydramnios AFI < 5 cm, and 36% had reduced liquor AFI : 6-10 cm.

WEIGHT GAIN



Distribution of cases based on Amniotic fluid Index

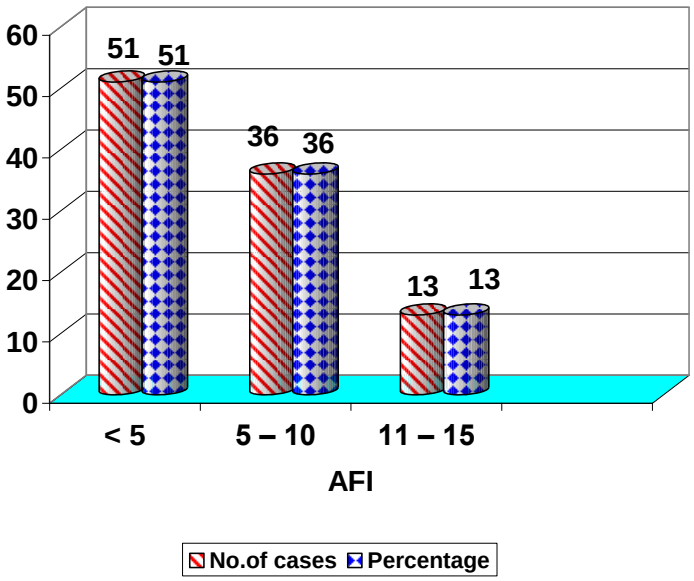


Table – 7

Distribution of cases based on Umbilical artery

Doppler changes

Umbilical artery Doppler changes	Frequency	Percentage
Normal flow	34	34
Reduced flow	34	34
Absent flow	28	28
Reversal of flow	4	4
Total	100	100

As shown in the table and pie chart, out of 100 cases 34 had normal flow, 34 had reduced flow, 28 had absent diastolic flow. The rest 4 had reversal of flow.

Umbilical artery Doppler changes

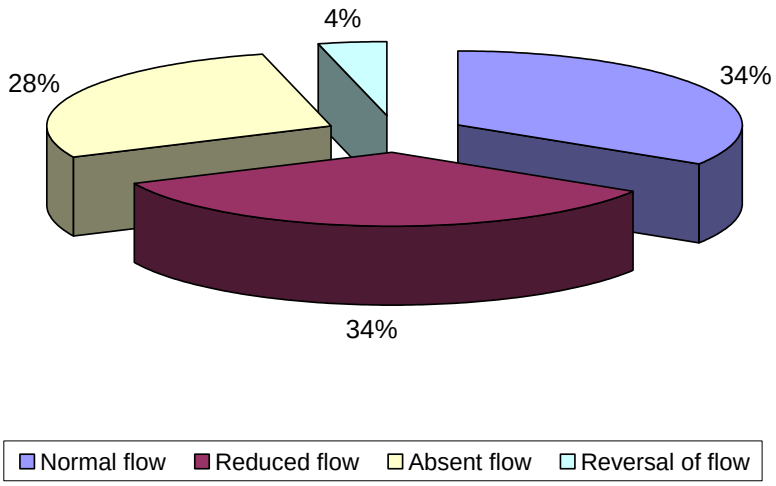


Table – 8

Distribution of cases based on Macroscopic Abnormalities

Macroscopic Abnormalities	Frequency	Percentage
Present	34	34
Absent	66	66
Total	100	100

As shown in the table and pie chart, 66% had normal macroscopy, the remaining 34% had one or more of the following abnormalities. Calcification, unduly small placenta, necrosis, retroplacental clots.

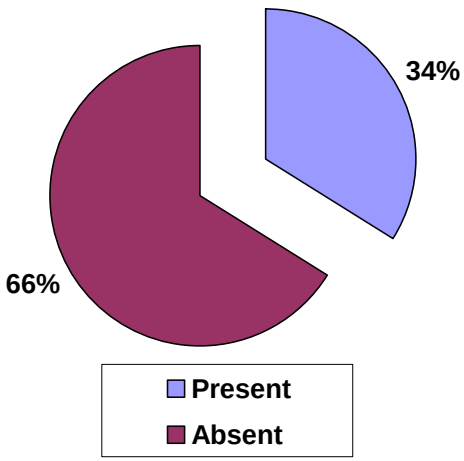

Macroscopic Abnormalities
34%
66%
Present
Absent

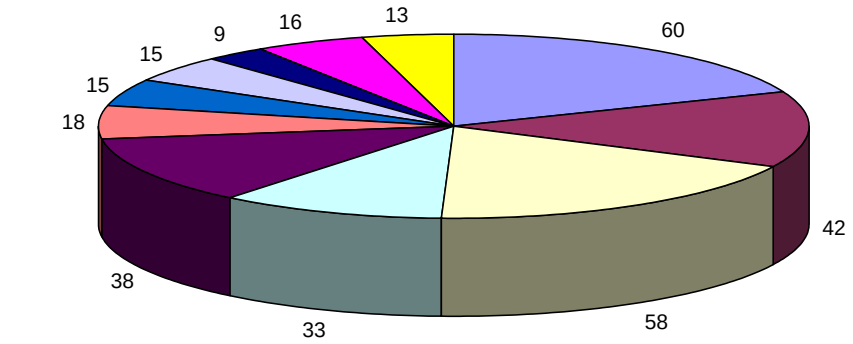
Table – 9

Based on Microscopic abnormalities of placenta

Placental histopathology	Frequency	Percentage
Placental Infarcts	60	60
Decidual vasculopathy	42	42
Syncytial knots	58	58
Chorioamnionitis	33	33
Stromal fibrosis	38	38
Chronic villitis	18	18
Hemorrhagic endovasculitis	15	15
Increased Trophoblastic proliferation	15	15
Increased perivillous fibrin	9	9
Basement membrane thickening	16	16
Calcifications	13	13

As per the table and pie chart placental infarcts were found in 60%, syncytial knots in 58%, decidual vasculopathy in 42%, the remainder being chorioamnionitis 33%, stromal fibrosis 38%, chronic villitis 18%, hemorrhagic endovasculitis 15%, basement membrane thickening 16%, calcification 12%. Increased trophoblastic proliferation in 15% of cases.

Microscopic abnormalities of placenta



- Placental Infarcts
- Duodenal vasculopathy
- Syneytial knots
- Chorioamnionets
- Stromal fibrosis
- Chronic villitis
- Hemorrhagic endovasculitis
- Increased Trophoblastic proliferate
- Increased perivillous fibrosis
- Basement membrane thickening
- Calcifications

Table – 10

Based on number of placental lesions

No.of Lesions	Frequency	Percentage
1	6	6
2	11	11
3	39	39
≥4	44	44
Total	100	100

Among 100 cases, 44 had more than or equal to 4 placental lesions, 39 had 3 lesions, 11 had 2 lesions and only 6 had single lesion.

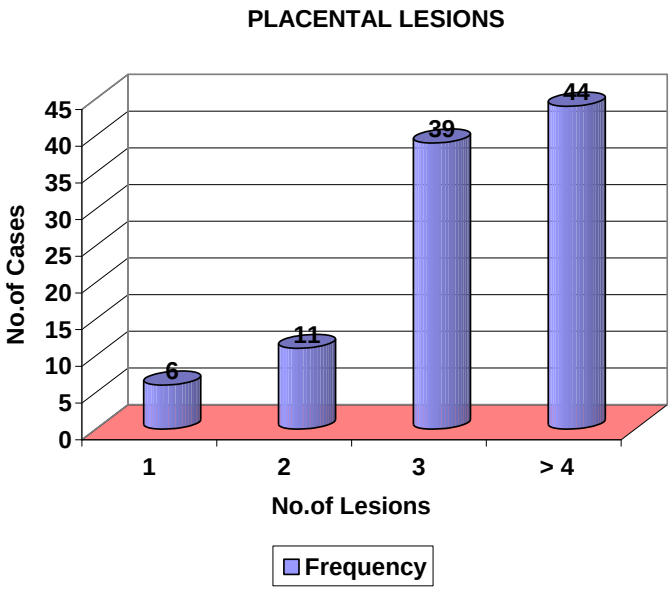

PLACENTAL LESIONS
No.of Cases
45
40
35
30
25
20
15
10
5
0
6
11
39
44
1
2
3
> 4
No.of Lesions
Frequency

Table – 11

Comparison of umbilical artery Doppler waveforms with placental pathology

Doppler waveforms	No.of placental lesions				
	1	2	3	4	Total
Abnormal flow	1(1%)	2(2%)	27(27%)	36(36%)	66
Normal flow	5(5%)	9(9%)	12(12%)	8(8%)	34
Total	6	11	39	44	100

Increased number and frequency of placental pathologies were more commonly observed in cases with abnormal Doppler waveforms when compared with normal Doppler waveforms with difference being statistically significant with $p < 0.001$.

Comparison of umbilical artery Doppler waveforms with placental pathology

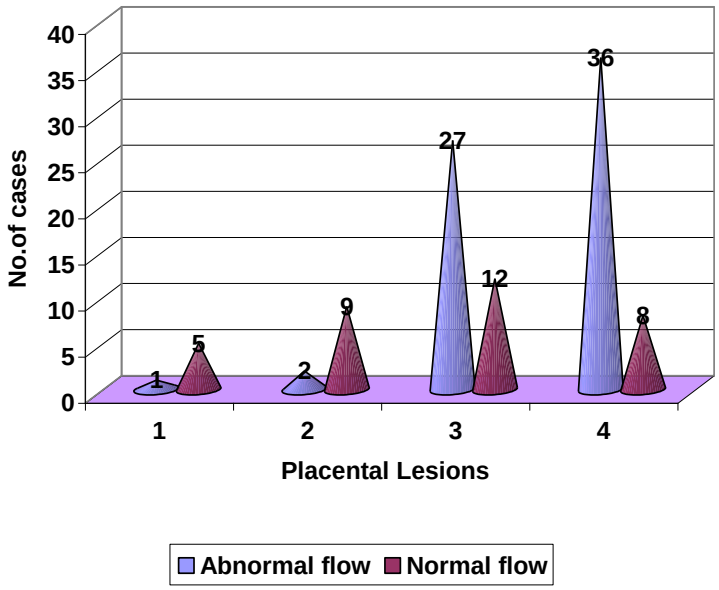


Table-12
Abnormal Doppler waveforms in relation to the number of Placental lesions

No of placental lesions	Reduced diastolic flow	Absent flow	Reversal of flow	Total
1	1(1.5%)	-	-	1
2	1(1.5%)	-	1(1.5%)	2
3	13(19.6%)	13(19.6%)	1(1.5%)	27
≥4	19(28.7%)	15(22.7%)	2(3%)	36
Total	34	28	4	66

Out of the 66 cases with Doppler abnormalities, 27 cases had 3 lesions and 36 of them had four or more lesions. ($p < 0.001$) significant.

Table – 13

Distribution of cases based on type of Delivery

Mode of Delivery	Frequency	Percentage
Vaginal	46	46
Instrumental	4	4
LSCS	50	50
Total	100	100

As mentioned above, 46% had vaginal delivery, 4% had instrumental delivery, 50% were delivered by LSCS.

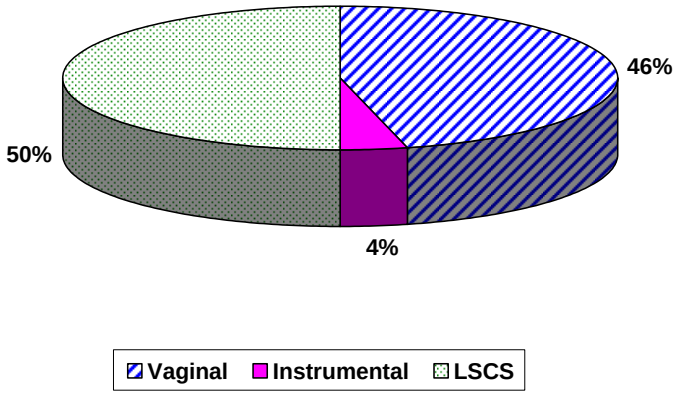
Table – 14

Based on weight of the placenta

Weight of placenta	Frequency	Percentage
≤350	51	51
350 – 400	39	39
≥400	10	10
Total	100	100

As stated above 51% of the study group had placental weight <350 grams, 39% had placental weight between 350-400 grams.

MODE OF DELIVERY



Based on weight of the placenta

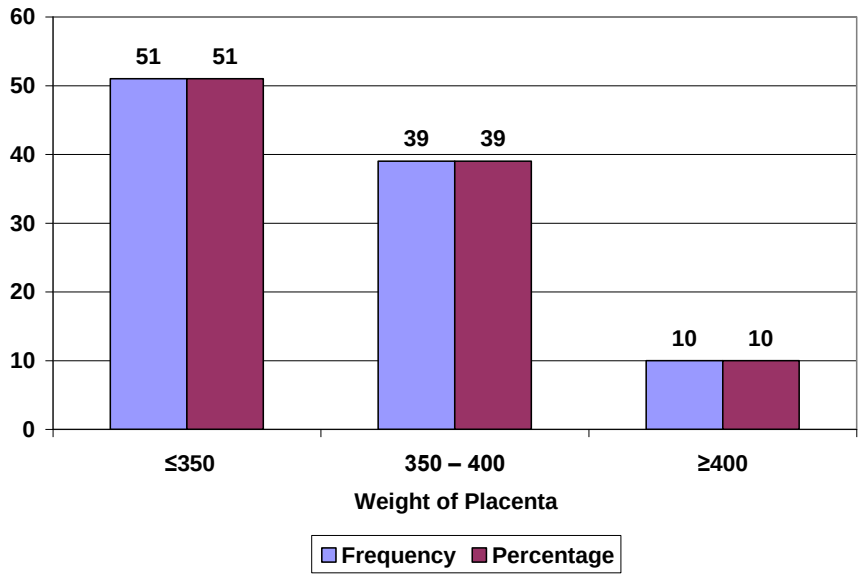


Table 15

Distribution based on weight of the baby

Weight of baby	Frequency	Percentage
<1.5 kg	6	6
1.5-2kg	51	51
2.1-2.5kg	43	43
>2.5kg	-	-
Total	100	100

43 babies had birth weight between 2.1-2.5 kg (<10th percentile), 51 babies had birth weight between 1.5-2 kg (<5th percentile), the remaining 6 babies had birth weight less than 1.5 kg.

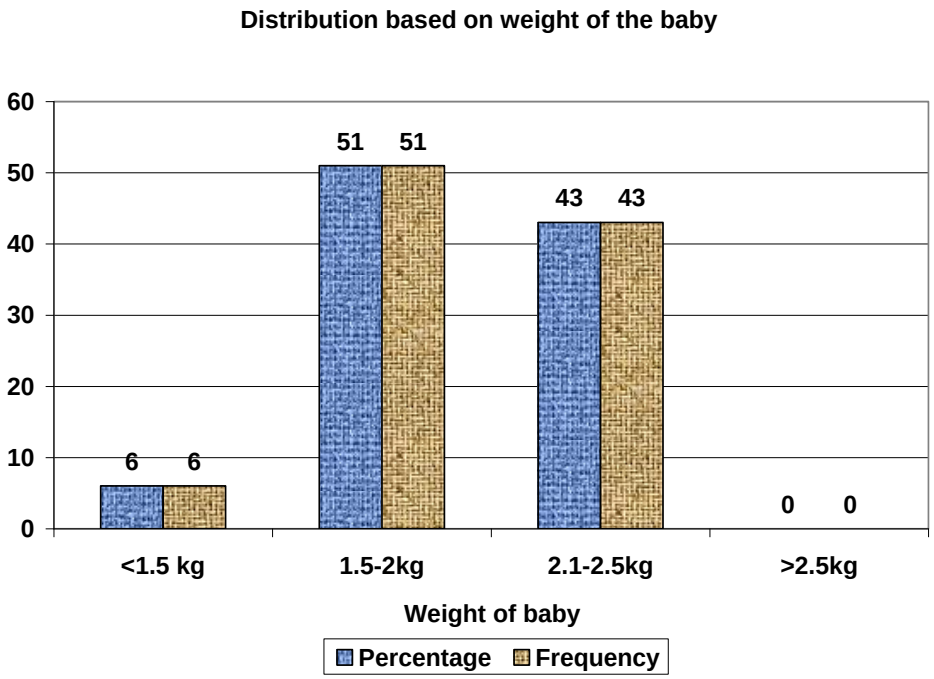

Distribution based on weight of the baby
60
50
40
30
20
10
0
6
6
51
51
43
43
0
0
<1.5 kg
1.5-2kg
2.1-2.5kg
>2.5kg
Weight of baby
Percentage
Frequency

Table 16

Comparison of Birth weight and placental weight in relation to No.of placental lesions.

No.of lesions	Birth weight Mean(grams)	Placental weight Mean(grams)
1	2340	410
2	2130	400
3	2060	350
≥ 4	1820	330

The total cumulative number of placental lesions had a significant correlation with placental birth weight and fetal weight. As the number of lesions increases the birth weight and the placental weight decreases, the relation being statistically significant with p value <0.001.

Comparison of Birth weight and placental weight in relation to No.of placental lesions.

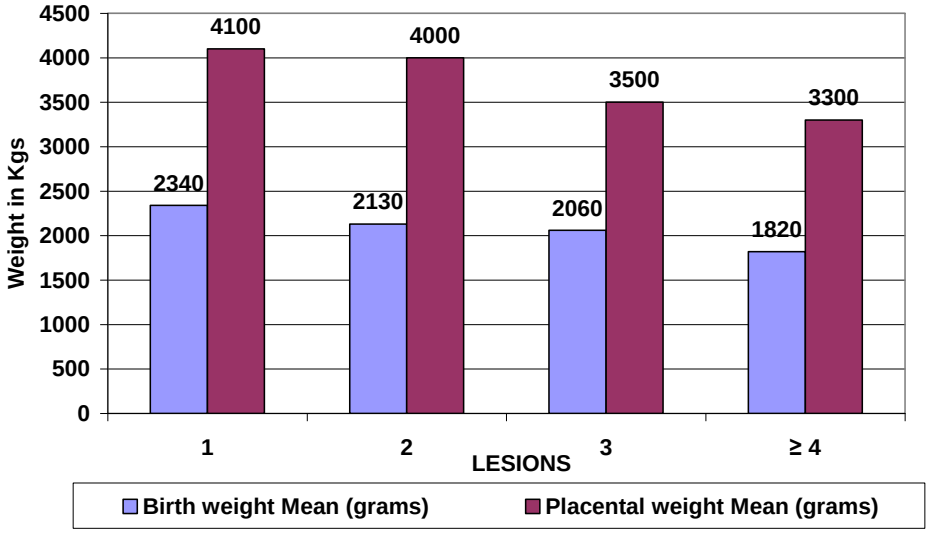


Table – 17

Fetal outcome in relation to number of placenta lesions

No.of lesions	Apgar (Median)		Neonatal complications			
	1”	5”	HIE	RDS	MAS	Sepsis
1	7	8	0	0	0	1(1.2%)
2	6	8	0	3(3.8%)	2(2.5%)	1(1.2%)
3	5	7	4(5.1%)	12(15.3%)	10(12.8%)	1(1.2%)
>4	2	4	4(5.1%)	18(23%)	18(23%)	4(5.1%)
Total			8	33	30	7

Increased number of placental lesions was associated with a decreased fetal apgar score and increased frequency of neonatal complications.Babies with single placental lesion had a 1 min apgar score of 7 compared to 2 for babies having 4 or more lesions. Similarly the rate of neonatal complications increased significantly when number of lesions were more than 4($p<0.001$)

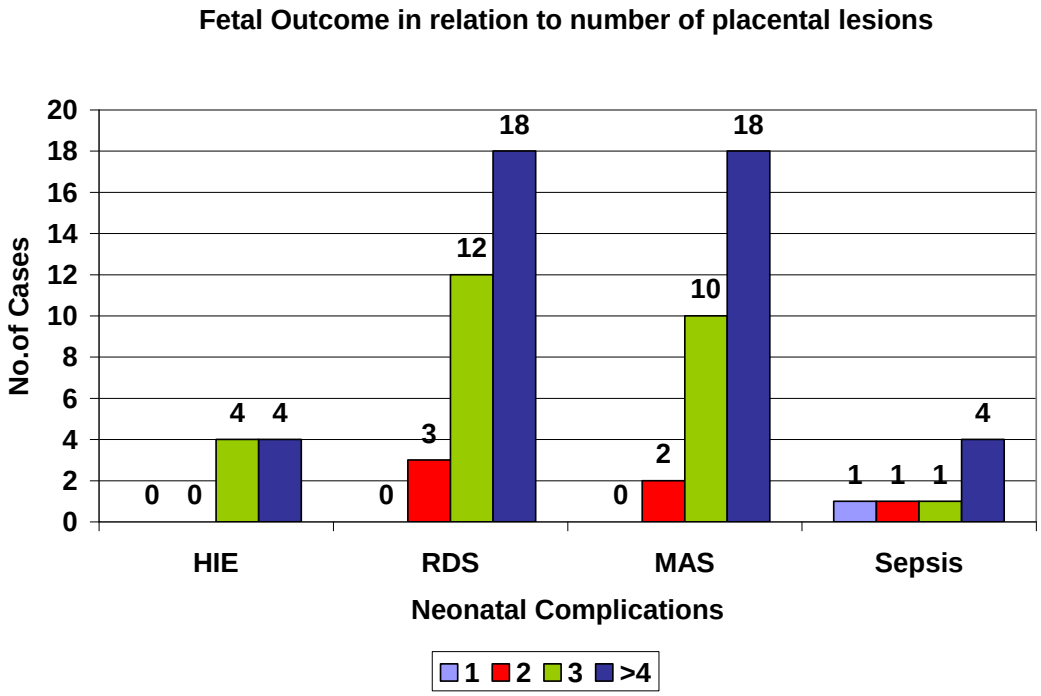

Fetal Outcome in relation to number of placental lesions
No.of Cases
20
18
16
14
12
10
8
6
4
2
0
0 0 4 4
0 3 12 18
0 2 10 18
1 1 1 4
HIE
RDS
MAS
Sepsis
Neonatal Complications
1 2 3 >4

Table 18

Number of placental lesions in relation to perinatal mortality

No of placental lesions& frequency		Doppler abnormalities	Still birth	Admission in NICU	Neonatal death
1	6%	1	0	6 (min-2days Max-3 days)	0
2	11%	2	0	11 (min-2 days Max-5 days)	0
3	39%	27	0	39 (min-4 days Max-21days)	5
≥4	44%	36	3	41 (min 5 days Max-28 days)	11
Total	100	66	3	97	16

Out of 100 cases, 83 cases had 3 or more placental abnormalities.Out of 66 cases with Doppler abnormalities,63 cases had 3 or more placental lesions.3 babies were still born who had ≥4 placental lesions, 16 cases of neonatal death of which 5 babies had 3 lesions and 11 babies had >4 placental lesions.

Figure - 1

Gross examination of the placenta showing yellow areas of infarction

Figure No. 2

Hypertrophic decidual vasculopathy

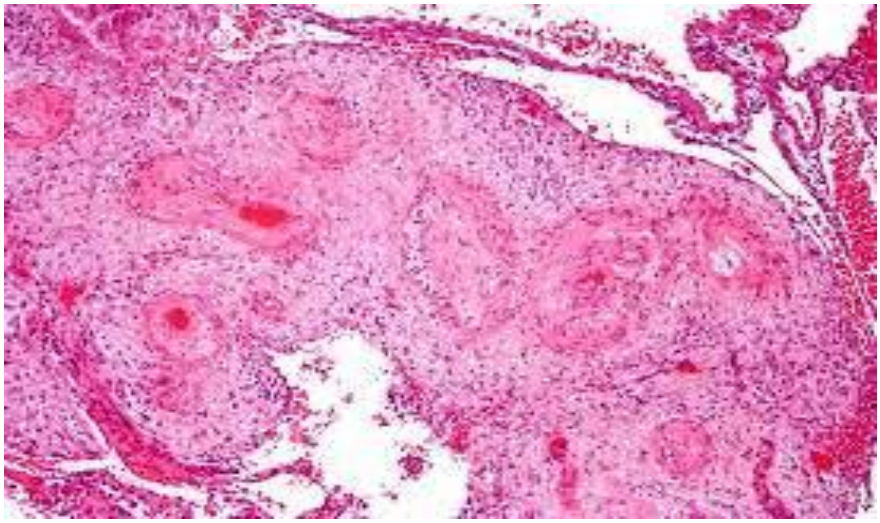


Figure No. 3

Microscopic examination showing calcification

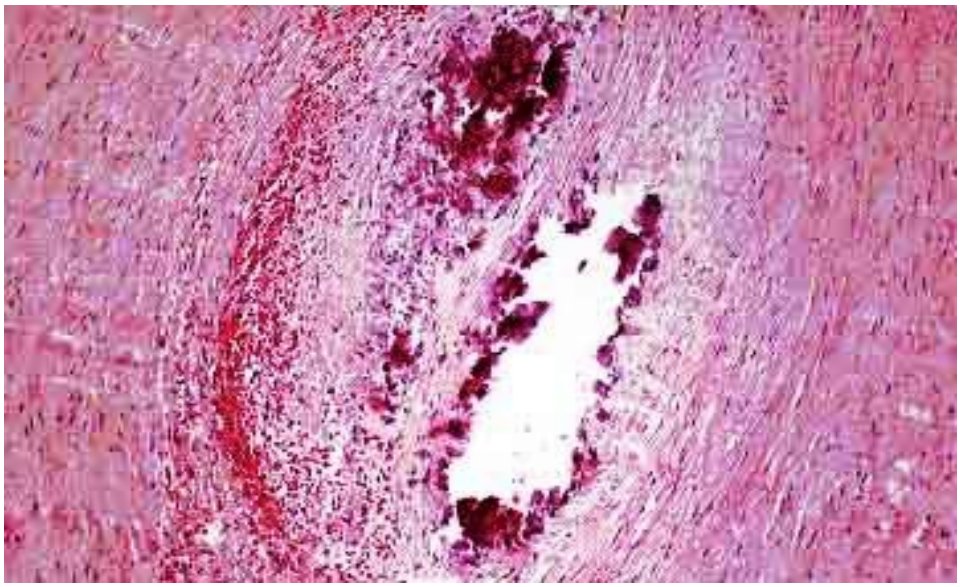


Figure No. 4

Thrombotic vasculopathy

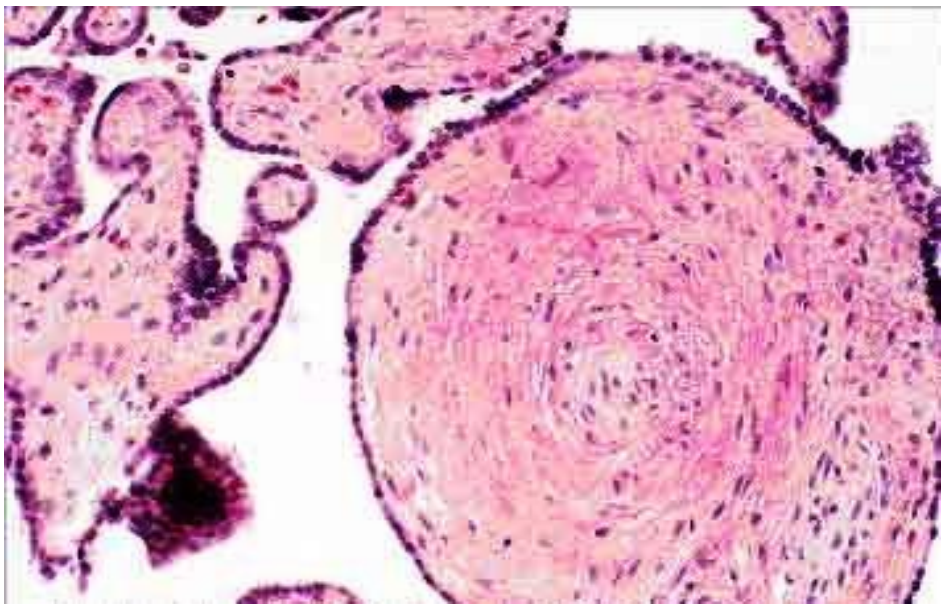


Figure No. 5

Stromal fibrosis

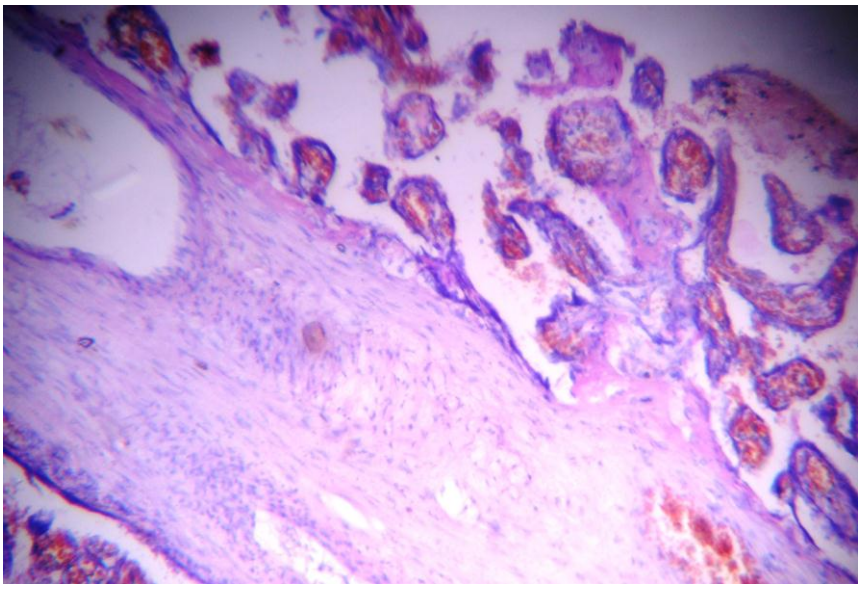


Figure No. 6

Chorioamnionitis

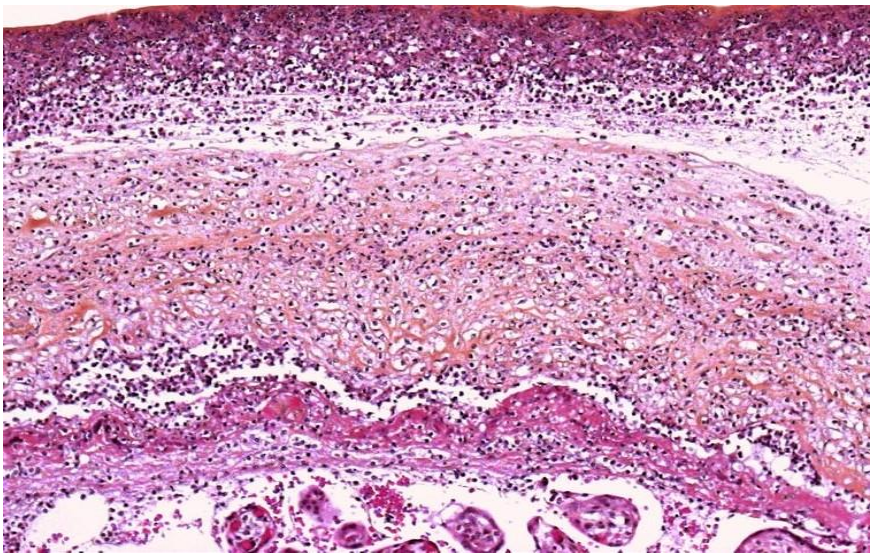
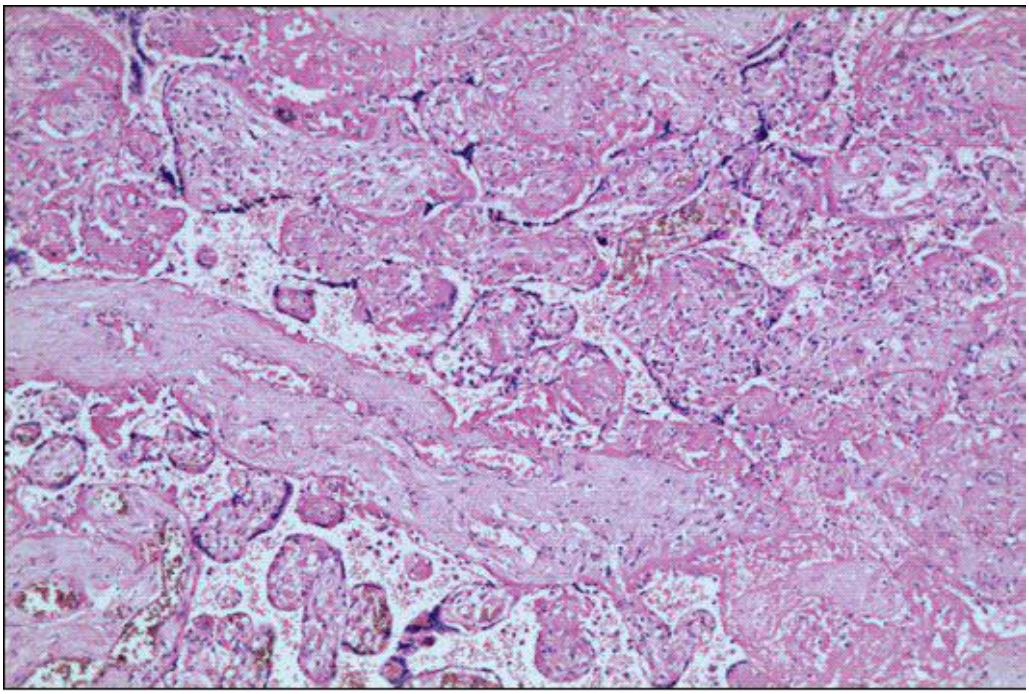


Figure No. 7

Villitis of unknown etiology



SUMMARY

IUGR is related to a variety of clinicopathologic factors including maternal, uterine and fetal factors. Preeminent among the maternal factors is the restriction of growth due to uteroplacental insufficiency. Recent studies of placental examination of IUGR pregnancies provide good evidence for the occurrence of distinctive structural and histological abnormalities.

In this study, majority of cases were primiparous women (48%) in the age group of 21-30 years(80%).A study by Robert M.Kliegman et al showed that low socioeconomic status have been associated with poor fetal nutrition. About 58% of patients belong to class V socioeconomic status and 30% belong to class IV socioeconomic status.

In this study, 45% cases of IUGR are of unexplained etiology and PIH contributed to 28%.Park et al,Kim et al,Chun et al 2002 showed that IUGR groups had higher incidence of oligohydramnios than controls.Our study proved similar results.

In this study, 34% of cases had macroscopic abnormalities of placenta. The placentas from pregnancies complicated by IUGR tend to be smaller than those from normal uncomplicated

pregnancies. (Thame et al 2001, 2004, Khadija qamar et al). In the present study, the placental weights were significantly lower especially in those with 3 or more number of placental lesions.

Macara et al worked on the structural analysis of placental villi from growth restricted pregnancies with abnormal umbilical artery Doppler waveforms. They found that the terminal villi from the IUGR cases were smaller in diameter than those of controls and had increased syncytial nuclei, thickened basal lamina and increased stromal deposition of collagen and fibrin. In our study, the 5 main histopathological lesions documented are placental infarcts (60%) which are mainly due to ischaemia followed by syncytial knots in 58% of patients, decidual vasculopathy in 42% of patients, stromal fibrosis in 38% and chorioamnionitis (33%).

The overall incidence of infarction is increased in placentas growth restricted infants. (Bjoro et al, Suska et al, Salafia et al) and Laurini et al have claimed that infarction is the only placental lesion that correlates with growth restriction. In our study, 60% of babies had placental infarct.

The finding of ischemic type changes in many placentas from pregnancies with Idiopathic intrauterine growth restriction suggests

that there is diminished maternal blood flow in such cases and this has been confirmed by Doppler studies of uteroplacental circulation. (Trudinger et al, Mc Cowarr et al, Jacobson et al, Beroley et al, Schulmann et al, Iwata et al, Nicolaides et al). There is a clear correlation with abnormal Doppler wave form and the presence of ischemic type of changes in the placenta. In our study, increasing number of placental lesions had significant correlation with abnormal Doppler wave forms.

Placental pathology and its relation to perinatal outcome

Liaquat All minnas et al,Muhammad yunas khan et al: 2009 showed that mean birth weight was lower in fetus with multiple placental abnormalities. Majority of babies (57%) had low birth weight with mean birth weight of 2.06 kg when there are 3 lesions and a mean of 1.82 kg when there are 4 or more lesions.

A study by Rose M. Viscardi et al and Chen Cin J. Sun et al has proved that severity of placental abnormalities expressed as the cumulative number of lesions is a significant risk factor for IUGR and increased perinatal mortality. Our study proved the similar results.

Increased number of placental lesions were associated with a decreased fetal apgar score and increased frequency of neonatal complications.Babies with single placental lesion had a 1 min apgar score of 7 compared to 2 for babies having 4 or more lesions. Similarly the rate of neonatal complications increased significantly when number of lesions were more than 4($p<0.001$)

The perinatal mortality increased with number of placental lesions. All the 3 cases of stillbirth were with multiple lesions. There were 16 cases of neonatal death with 3 or more lesions.

Assessment of placental pathology is an invaluable tool in determining the pathophysiology behind the growth restriction. It is also useful in determining the underlying mechanisms leading to pregnancy complications and for guiding future investigations.

The consequences of aberrant fetal growth secondary to placental dysfunction extend beyond the intrauterine phase of existence. A variety of adult chronic illness including cardiovascular disease, dyslipidemia, type II diabetes, obesity are now felt to be manifestations of fetal malnutrition usually resulting from placental changes precluding optimum function. Therefore

placental examination may represent a means of investigating the intrauterine past to explain the present condition of the neonate. The results of this study provide new evidence for the relationship between intrauterine events, reduced growth velocity and postnatal consequences. Specific patterns of placental pathological findings may be predictive of specific adverse neonatal outcomes.

Over the past 10-15 years medicolegal implications of placental pathologic examination have been emphasized. In obstetric malpractice ligations involving perinatal death, neurologic damage or mental impairment, the presence of chronic placental abnormalities (such as infarcts, small placental size, membranous cord insertion, maternal decidual vasculopathy, chorangiosis, nucleated fetal RBCS etc) may suggest that fetal damage occurred antenatally rather than perinatally. A recent analysis of obstetric malpractice claims concluded that ‘many more neurologically impaired infant claims could be successfully defended if placenta specimens were available for examination at the time a claim is made’.

CONCLUSION

1. Histopathological examination of placenta in cases with IUGR revealed pathological changes like infarction, inflammation and fetal thrombotic vasculopathies.
2. Increased frequency of placental lesions and increased number of lesions were significantly associated with IUGR.
3. Increased number of placental lesions was commonly observed in cases with abnormal Doppler waveforms compared with normal Doppler waveforms with difference being statistically significant with p value < 0.001.
4. Multiple placental lesions were associated with low birth weight, low placental weight and increased frequency of neonatal complications and increased perinatal mortality.($p<0.001$)
5. It is well recognized that all institutions do not have pathologist with experience in doing placental pathology. If protocols are instituted such that placentas from all cases of IUGR are subjected to histopathological examination, it will allow a more complete understanding of the pathophysiology of fetal growth restriction, knowledge of risk of additional complications to the mother and the neonate and the risk of recurrence in subsequent pregnancies.

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PROFORMA

PLACENTAL PATHOLOGY IN IUGR AND ITS RELATION TO PERINATAL OUTCOME

Case No. : IP No. :

Name : D.O.Admission:

Age : D.O. Delivery :

Husband's Name :

Occupation : Husband Educational Husband

Wife Wife

Socioeconomic Status :

Monthly Income : < 5000 / 5000 – 8000 / 8000-10000 / > 10000

Presenting Complaints :

Safe confinement / Pains / Draining PV / Bleeding PV

Menstural H/o : Cycles : Regular / Irregular

Marital H/o : Married since _____ month

Consanguineous / Non consanguineous

Present Obstetric H/o : Obstetric Code : Primi

LMP : Booked at GRH / Booked outside

EDD : Pregnancy weight gain :

First Trimester scan EDD Risk Factors :

Past Obstetric H/o :

LCB :

H/o PIH / GDM / Prolonged pregnancy / Malnutrition

Mode of Delivery: LN / Outlet / Vacuum / LSCS

Outcome :

Baby weight

Term / Preterm / IUGR

Still born / living / dead

Past H/o

Preeclampsia	:	Cardiac disease class 3,4	:
Chronic HT	:	Connective tissue disorders:	
Chronic renal disease:		Hemoglobinopathies	:
Diabetes mellitus	:	Sickle cell Anaemia	:
Epilepsy	:	Multiple gestations	:
Chronic lung diseases:		Living at high altitude	:

Personal H/o

Husband Smoker	:
Tobacco chewing	:
Alcohol ingestion	:
Drug intake	:
Drug addiction	:

General Examination

Height	:	PR	:
Weight	:	BP	:
Pallor	:	Thyroid	:
Cyanosis	:	Breast	:
Clubbing	:	CVS	:
Pedal edema	:	RS	:

Obstetric Examination :

Estimated gestational age	:
Height of the uterus	:
Symphysiofundal height	:
Abdominal girth	:

Investigations :

Hb %	:

Blood Grouping & Typing:

Random blood sugar :

Urea :

Creatinine :

Urine Albumin :

Sugar :

Deposits :

PPTCT :

USG

Gestational age :

AFI :

EFW :

FL / AC :

HC / AC :

Congenital anamolies :

Placental grading :

Doppler :

Type of IUGR :

Labour Induction :

Spontaneous / ARM / Gel / Syntocinon / Misoprostol

Intranatal course :

1st stage : Uneventful /prolonged

2nd stage : Uneventful / prolonged

Mode of Delivery

Labour Natural :

Forceps / Vaccum : Indication :

LSCS : Indication :

Outcome of Delivery :

Live birth / Still birth :

Sex :

Apgar 1" : Apgar 5":

Weight of the baby :

Length of baby :

Ponderal Index :

Meconium : Thin / Thick

IUGR : Symmetrical / Asymmetrical

Neonatal Complications :

Birth asphyxia :

Jaundice :

Sepsis :

Admission in NICU :

Ventilatory support :

Neonatal Death :

Macroscopy

Colour : Calcification :

Texture : Atrophy :

Dimension : RP Clots :

Weight : Abnormalities :

Thickness : Placentary Index :

Microscopy :

Chorioaminionitis :

Placental Infarcts :

Perivillous fibrin Deposits :

Chronic villitis :

Decidual vasculopathy :

Stromal fibrosis :

Syncytial knots :

Hemorrhagic Endovasculitis :

Increased Trophoblastic proliferation :

Basement membrane thickening:

Placental lesion score

MASTER CHART

S.No.	IP NO	AGE	PARITY	INCOME	ETIOLOGY	WT GAIN	AFI	DOPPLER	PLACENTA MACROSCOPY	PLACENTA MICROSCOPY	LESIONS	MODE OF DELIVERY	PLACENTA WEIGHT	BABY WT	CONDITION AT BIRTH	NNC
1	17042	2	3	1	3	2	2	1	2	1	1	1	3	3	1	1
2	15474	2	2	1	7	2	1	2	1	1,2,5,7	4	3	1	2	1	1
3	15915	3	2	1	3	2	1	3	1	1,3,5,7	4	3	1	2	1	1
4	16565	2	3	1	6	2	1	4	2	2,4,5,7	4	3	1	2	1	1
5	14553	2	2	1	1	3	2	1	1	1,3,5	3	3	2	3	1	1
6	14490	3	1	1	2	2	2	1	2	1,6,7	3	3	2	2	1	1
7	17514	2	3	1	6	2	1	2	2	1,2,3,4	4	3	1	2	1	1
8	16676	2	1	1	2	2	2	1	2	1,3,5	3	3	2	3	1	1
9	18907	2	2	3	1	2	2	1	2	1,2,3,5	4	1	1	3	1	1
10	18190	2	2	2	1	3	2	2	2	1,3,4,5	4	1	1	3	1	1
11	20067	3	2	2	1	3	2	1	2	1,3,7	3	3	2	3	1	1
12	15643	1	3	1	3	2	1	2	2	1,6,7	3	1	2	2	1	1
13	5968	2	3	1	1	2	1	3	1	1,2,4,7	4	1	1	3	1	1
14	18659	2	2	1	4	2	1	3	1	3,4,5,6	4	2	2	2	1	1
15	19142	2	3	1	5	2	2	1	2	7	1	3	2	3	1	2
16	17459	2	1	1	2	3	1	2	2	1,2,3,4	4	3	1	2	1	1
17	15927	2	1	4	2	2	2	1	2	2,3,7	3	3	1	3	1	1
18	15018	2	2	2	1	2	2	1	2	2,6,7	3	3	1	2	1	1
19	5888	2	1	2	1	3	1	2	2	1,3,4,5	4	3	1	2	1	1
20	7009	2	1	2	1	2	1	2	2	3,4,5,6	4	3	2	3	1	1
21	6216	2	1	2	7	2	1	2	2	1,4,7	3	3	2	2	1	1
22	5982	2	1	1	2	2	1	2	2	3,4,5,7	4	3	2	2	1	1
23	7859	3	1	2	1	3	1	1	1	1,3,4,5,6,7	4	3	1	1	1	1
24	7850	2	2	3	1	2	3	1	2	2,3,4,7	4	3	1	2	1	1
25	7296	2	1	1	2	2	3	1	2	1,2,3,4,7	4	3	1	2	1	1

26	8051	2	1	2	1	3	1	1	1	1,2,3,5,6	4	3	1	2	1	1
27	8321	2	2	1	1	2	3	1	2	2,3,4,7	4	3	1	2	1	1
28	19239	2	2	2	1	2	1	3	1	1,3,7	3	3	2	2	1	1
29	9151	2	1	4	2	2	2	1	1	1,3,4,7	4	3	1	2	1	1
30	10734	2	1	2	3	2	2	1	2	1,2,3,5,7	4	3	2	2	1	1
31	18627	2	4	1	3	2	1	3	1	1,2,3,4,5,7	4	3	1	2	1	1
32	16400	2	1	1	2	2	2	1	2	1,4	2	3	3	2	1	1
33	15596	2	1	2	1	3	1	3	1	1,3,4	3	3	2	3	1	1
34	21016	2	3	1	1	3	2	1	2	1	1	1	2	3	1	2
35	14653	2	1	2	1	3	1	2	1	1,2,3,7	4	1	1	3	1	1
36	13920	2	2	3	1	2	3	3	2	2,3,4,5,7	4	3	1	2	2	0
37	31363	2	1	1	2	2	2	1	2	1,2,5	3	3	2	3	1	2
38	14422	2	1	2	1	3	1	2	2	1,2,3,4,7	4	3	1	3	1	1
39	8865	1	1	1	3	2	3	3	1	1,2,3,7	4	3	2	2	1	1
40	9761	2	1	1	3	2	2	2	2	1,2,3,7	4	3	2	3	1	1
41	9343	2	2	4	2	2	1	4	1	2,4,	2	3	2	3	1	1
42	9905	2	2	1	3	2	2	3	2	1,2,3,4,7	4	3	1	2	1	1
43	11303	2	1	2	1	2	3	2	2	1,2,3,7	4	3	1	3	1	1
44	11487	2	1	3	1	2	3	2	1	1,2	2	3	2	2	1	1
45	12067	2	1	2	1	2	1	2	1	1	1	3	3	3	1	2
46	12107	2	2	3	1	2	3	3	2	2,3,4,5,7	4	3	2	3	1	1
47	12235	2	1	1	2	2	2	1	2	2,3,7	3	3	1	3	1	1
48	15689	2	3	2	2	3	1	2	1	1,3,5	3	1	2	3	1	1
49	15462	2	4	1	3	1	2	1	2	1	1	1	3	3	1	2
50	18243	2	4	1	3	2	2	3	2	1,2,4,7	4	1	1	2	1	1
51	20064	2	3	2	3	2	1	3	1	2,4,7	3	1	1	3	1	1
52	20023	2	3	1	4	2	1	3	1	2,4,7	3	1	3	2	1	1
53	20300	1	3	1	1	2	3	1	2	1,7	2	1	3	3	1	1
54	19059	2	3	1	1	2	3	1	2	3,7	2	1	3	2	1	1
55	26300	2	3	1	1	2	3	1	2	4,6	2	1	2	3	1	1
56	20306	2	1	1	2	2	1	2	2	3,4,7	3	1	1	2	1	2
57	15603	2	2	1	3	2	2	2	2	2,4,7	3	1	2	2	1	1
58	21071	2	3	1	1	2	1	2	2	3,4,5,7	4	1	1	3	1	1
59	20274	2	2	1	7	2	2	2	1	4,6,7	3	1	2	1	1	1

60	19867	2	2	1	3	2	2	1	2	2,7	2	1	1	2	1	2
61	20129	1	2	1	1	2	1	3	1	2,4,7	3	1	1	3	1	1
62	20755	1	2	2	1	3	2	1	2	4,7	2	1	3	2	1	2
63	20588	2	2	2	1	3	2	1	2	1,2	2	1	2	3	1	2
64	18467	2	1	1	2	2	2	1	2	1,4	2	3	3	3	1	2
65	7402	3	2	1	1	2	1	3	1	1,3,5	3	3	1	2	1	1
66	16420	2	1	1	2	2	3	1	2	5,6	2	3	2	2	1	2
67	24136	2	1	1	2	2	1	2	2	1,3,5,7	4	1	2	2	1	1
68	19090	2	3	1	1	2	1	2	2	1,4,6,7	4	1	1	2	1	1
69	18065	1	4	1	2	3	1	3	2	1,3,4,6,7	4	1	1	2	1	1
70	14553	2	2	2	1	3	2	3	2	4,1,2	3	3	2	3	1	1
71	15018	2	2	2	1	3	2	2	1	2,3,5	3	3	2	3	1	1
72	21372	2	1	2	1	2	1	4	2	1,3,5,7	4	1	1	3	1	1
73	19681	2	1	1	2	2	1	2	2	1,2,5,6	4	1	1	3	1	1
74	19682	1	1	1	2	2	1	2	2	2,3,4,6	4	1	1	2	1	1
75	19950	2	2	1	1	2	1	4	1	1,5,7	3	1	2	3	1	1
76	14409	1	1	4	2	2	2	3	2	1,2,3,4,7,7	4	3	1	1	2	0
77	8471	2	3	1	3	2	2	2	2	1,2,4,5	4	1	1	3	1	1
78	20650	2	2	1	2	2	1	2	2	1,7,7,7	4	1	1	2	1	1
79	18568	2	2	1	6	2	1	2	2	1,2,3,4	4	1	1	1	1	1
80	20666	2	3	1	5	2	2	1	2	1	1	1	3	3	1	2
81	18735	2	2	1	4	2	1	3	1	3,5,7,7	4	2	1	2	1	1
82	16100	2	2	1	1	2	1	3	2	1,3,4,7	4	1	1	2	1	1
83	18140	2	2	3	1	2	1	3	2	4,6,7,7	4	1	1	1	1	1
84	18192	2	2	4	1	2	1	3	2	1,3,4,5	4	1	1	1	2	0
85	14742	1	1	1	2	2	1	3	1	2,4,7	3	1	2	3	1	1
86	13908	1	1	2	1	3	1	3	1	1,3,4	3	3	1	3	1	1
87	14811	2	1	1	2	2	2	1	2	1,4,5	3	1	1	2	1	1
88	13490	1	1	2	1	3	1	2	2	1,7,7	3	1	1	2	1	1
89	14675	2	1	3	1	2	4	2	1	1,5,7	3	1	1	2	1	1
90	13981	2	1	2	1	2	1	2	1	4,5,7	3	3	2	3	1	2
91	13987	2	1	2	4	2	1	2	1	1,3,5	3	2	1	2	1	1
92	14199	2	1	2	1	3	1	2	1	1,5,7	3	1	2	2	1	2
93	14454	2	1	2	1	2	1	3	1	1,4,7	3	1	1	3	1	2

94	14409	1	1	1	2	2	1	1	2	1,2,6	3	3	2	3	1	2
95	14407	2	1	2	1	3	1	2	2	1,3,6	3	3	2	3	1	2
96	13908	1	1	1	2	2	2	1	2	1,2,5	3	3	2	2	1	2
97	14742	1	1	1	2	2	2	3	2	1,2,6	3	1	2	2	1	2
98	15367	2	1	2	6	2	1	3	1	1,2,3	3	1	2	2	1	2
99	14354	1	1	1	2	2	2	3	1	1,3,6	3	2	2	2	1	2
100	15201	2	1	1	2	2	2	1	2	1,2,3	3	1	1	2	1	2

MASTER CHART SCALE

	1	2	3	4	5	6	7
Age	≤ 20	21-30	>30	-	-	-	-
Parity	1	2	3	Above 4	-	-	-
Socioeconomic status	V	IV	III	II & I	-	-	-
Etiology	Idiopathic	PIH	Anaemia	Heart disease	Placenta previa	Chronic maternal disease	Miscel laneous
Weight gain	< 5kgs	6-10 kgs	> 11 kgs	-	-	-	-
AFI	< 5cm	5-10 cms	11-15 cms	> 15 cms	-	-	-
Doppler	Normal flow	Reduced flow	Absent flow	Reversed flow	-	-	-
Macroscopic Abnormalities	Present	Absent	-	-	-	-	-
Microscopic Abnormalities	Infarct	Decidual vasculopathy	Syncytial knots	Chorioamnionitis	Stromal fibrosis	Chronic villitis	Miscella neous
Lesions	1	2	3	Above 4	-	-	-
Mode of Delivery	Vaginal	Instrumental	LSCS	-	-	-	-
Placental weight	<350 gms	350-400 gms	> 400 gms	-	-	-	-
Baby weight	< 1.5 kgs	1.5 – 2.0 kgs	2.1 – 2.5 kgs	> 2.5 kgs	-	-	-
Condition at Birth	Live	Still birth	-	-	-	-	-
Neonatal complications	Present	Absent	-	-	-	-	-

Ref.No. 6087/E4/3/2011

Govt.Rajaji Hospital,Madurai.20.
Dated: 10.10.2011

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The next Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 10.30 Am to 1.30Pm on 26.08.2011 at the Dean's Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have attend the meeting.

1.Dr.V. Ramanujam, M.D., D.P.M.,	M.S. i/c Govt.Rajaji Hospital,Madurai.	Convenor
2.Dr.N.Vijayasankaran,M.ch(Uro.)	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
3. Dr.P.K. Muthu Kumarasamy, M.D.,	Professor & H.O.D of Medical Oncology(Retired)	Member Secretary
4.Dr.T.Meena,MD	Professor of Physiology, Madurai Medical College	Member
5.Dr.Moses K.Daniel MD(Gen.Medicine)	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Thilshadh, MD(O&G)	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D.	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L.	Advocate, 623-B,II.Floor,East II Cross, K.K.Nagar,Madurai.20.	Member
10.Shri.O.B.D.Bharat,B.sc.,	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following projects were approved by the committee.

		Obstetrics and Gynecology M.M.C, Madurai.	Tocolysis in preterm labour.	
17	Dr.B.Madelin e vihya	PG Student in MD (General Medicine) M.M.C, Madurai.	Study of thyroid dysfunction in systemic lupus erythematosus	Approved
18	Dr.T.Latha Maheswari	PG Student in MD (General Medicine) M.M.C, Madurai.	Study of endometrial thickness by transvaginal sonography with histopathology correlation in abnormal uterine sleeding	Approved
19	Dr.P.K. Muthu kumaraswamy . D.M.	Professor and head of department M.M.C. Madurai.	Study of Docetaxel and Ramucirumab versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small Cell Lung Cancer Following Disease Progression after One Prior Platinum-Based Therapy....Swallowing diary Tamil Translation .	Approved
20	Dr.S. Sreeranjani	II year M.D OG M.M.C. Madurai.	Fetal Doppler Study of uterine, umbilical and Middle are bral artery as predictors of adverse perinatal out come in IUGR as my postgraduate thesis work.	Approved
21	Dr.J.Rekha	Post Graduate in M.D (O&G) M.M.C. Madurai.	Relationship of Placental Pathology to IUGR.	Approved
22	Dr.D. Meena	Post Graduate student in MD (O&G) Dept of Obstetrics and Gynecology M.M.C. Madurai.	Admission Test and it's correlation with perinatal outcome.	Approved
23	Dr.K. Karthikeyan	Post graduate student in General Medicine, VII Medical unit M.M.C, Madurai.	Serum magnesium and end organ damage in type 2 diabetes from April 2011 To October 2011.	Approved
24	Dr.J. Ramya	PG Student in MD (General Medicine) IV Medical Unit, M.M.C, Madurai.	Diastolic dysfunction in rheumatoid arthritils.	Approved
25	Dr. B.K. Bincy	PG Student in MD (General Medicine) II Medical Unit, M.M.C, Madurai.	Thyroid dysfunction in rheumatoid arthritis.	Approved
26	Dr. A. Shanmuga sundaram	Post graduate student in General Medicine, V Medical unit. M.M.C, Madurai.	Correlation of electrocardiography changes with prognosis in organophosphorus poisoning.	Approved
27	Dr.T.Gowari Thilagam,	Post-graduate in MD-Pharmacology (II year), M.M.C, Madurai.	Study of the drugs causing fixed eruptios.	Approved
28	Dr.M. Mathivani,	Post-graduate in MD-Pharmacology (II year), M.M.C, Madurai.	Study of Pattern of use and Adverse reactions to Anti snake venom.	Approved
29	Dr.T.Gowri thilagam	Post-graduate in MD-Pharmacology (II year), M.M.C, Madurai.	The effect of Pioglitazone on the distribution of body fat in type II Diabetic Patients.	Approved
30	Dr.S.Shankare swari	Post-graduate in Pharmacology M.M.C. Madurai.	Study on the adverse effects of steroids in patients with nephritic syndrome.	Approved

O.G.

31	Dr.S.RajeshKannan	Post graduate student in General Medicine II Medical unit M.M.C. Madurai.	Rreative protein (CRP) and angiographic correlation of disease in stemi and nstemi patients from April 2011 to October 2011.	Approved
32	G. Angala Eswari	Associate Professor in the PG and Research Department of Economics. Lady Doak College, Madurai.	Maternity Health Care Services at Public and Private Hospitals in Madurai District.	Approved
33	Dr.M. Mathivani	Post-graduate in MD Pharmacology (II year) Institute of Pharmacology, Madurai Medical College. Madurai.	To Study the pharmacoepidemiology of drugs therapeutically prescribed for the patients admitted for cataract surgery in Government Rajaji Hospital, Madurai.	Approved
34	Dr. Mathevan M.D. (Pediatrics)	Principal Investigator Meningitis surveillance Professor of Pediatrics Govt. Rajaji Hospital Madurai	Bacterial Meningitis Hospital based Sentinel Surveillance project.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work bto the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

MEDICAL SUPERINTEND 10/10/11

10/10/11

To

All the above members and Head of the Departments concerned.

All the Applicants.